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THE TREATMENT OF CHRONIC HUMAN AMEBIASIS WITH AUREOMYCIN*

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AS a part of a survey of intestinal parasites among veterans of World War II, every patient admitted to the Minneapolis Veterans Administration Hospital on the Medical Service during the first ten months of 1949 was asked to collect 3 random stool specimens to be examined for ova and parasites. In March, 1949, a young packing-plant employee, hospitalized for treatment of acute brucellosis with bacteremia due to *Brucella abortus*, was found to have trophozoites and cysts of *Endamoeba histolytica* in 3 successive stool specimens, although he at first denied any past symptoms of amebiasis. He was treated with oral administration of aureomycin because of his brucellosis, and it was noted with some surprise that within twenty-four hours amebae could no longer be found in his feces. Twenty-five formed and purged stool specimens were examined over the course of the next three months without disclosure of any trophozoites or cysts. This experience led us to explore the possibility that aureomycin might have a direct lethal effect upon *E. histolytica* and a beneficial effect in human amebiasis.

METHODS OF STUDY

In vitro studies.‡ Two strains of *E. histolytica* were studied. One was a stock strain obtained from the Department of Zoology of the University of Minnesota. The other was a strain freshly isolated from the feces of a patient (M.T. in Table 1). The effect of aureomycin on these cultures was investigated by two methods. The cultures were maintained by daily transfers onto liver-extract agar[1] slants overlaid with buffered 0.5 per cent saline solution (pH 7.4) containing a small amount of sterile rice powder. Aureomycin hydrochloride was dissolved in buffered saline solution and diluted serially by twofold dilutions from a concentration of 1000 microgm. per ml. to 0.15 microgm. per ml. Each dilution was overlaid on a liver-extract agar slant. A small amount of sterile rice powder and 0.1 ml. of a heavy suspension of a twenty-four-hour culture of amebae were added to each tube and to a control tube containing no aureomycin. The tubes were incubated at 37°C. At the end of twenty-four hours and again after forty-eight hours a loopful of sediment from each tube was examined microscopically for motile bacteria and trophozoites. Similar studies were also carried out with emetine hydrochloride and chloramphenicol.

The second method of study was as follows: A heavy suspension of a twenty-four-hour culture of *E. histolytica* was added to a series of tubes containing serial dilutions of aureomycin dissolved in warm buffered 0.5 per cent saline solution. After mixing, a portion of the contents of each tube was placed on a warm glass slide, covered with a glass cover slip and sealed with petrolatum. The slides were incubated at 37°C. and examined periodically under a microscope for motile bacteria and amebae. Identical experiments were also performed with freshly isolated strains of *Endamoeba coli* and *Endolimax nana*.

Clinical studies. The patients in this study, with two exceptions, were veterans of World War II who had presumably contracted amebiasis while serving outside the continental United States. After admission to the hospital complete histories were taken and thorough physical examinations were carried out. Three random stool specimens were examined by a trained parasitologist.§ The feces were emulsified in a 0.1 per cent solution of eosin in physiologic saline solution, and smears were made for microscopic examination. If suspected cysts or trophozoites were found, the feces were emulsified in D'Antoni's[2] iodine solution and a smear was made, sealed and examined carefully under the microscope. Every stool specimen was concentrated by Faust's[3] zinc-sulfate flotation method. If suspected cysts were found, the feces were emulsified in physiologic saline solution and

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§The parasitologic studies were carried out by Arthur I. Sanders under the direction of F. G. Wallace, Ph.D., associate professor of zoology, University of Minnesota.

stained with iron hematoxylin by the method of Diamond.[4] Each patient was examined prior to therapy by means of a sigmoidoscope. Mucus was aspirated from the bowel and immediately examined for trophozoites. Barium-enema examination, hematologic studies and a battery of liver-function tests were also performed. Aureomycin hydrochloride was then given orally; in most patients the dose given was 0.5 gm. every six hours for ten days. The aureomycin was usually given with tap water; in some patients milk was given with the drug in order to allay gastrointestinal side-effects. Antacids were not given. No other amebicidal drug was given with the aureomycin except in a few cases, which will be cited in detail. Random stool specimens were examined for ova and parasites during and at the conclusion of the therapeutic period. At least 3 stools were examined after a saline purge when the aureomycin had been discontinued. The patients were requested to return for re-examination at three-month intervals; all but 2 patients did so. Studies that revealed abnormalities (proctoscopy and so forth) prior to therapy were repeated. Each follow-up study included 3 to 4 stool examinations made after a saline purge.

TABLE 1. *Treatment of Human Amebiasis with Aureomycin at Minneapolis Veterans Administration Hospital, 1949: Chronic Amebic Dysentery.*

Case No.	Patient	Duration of Symptoms	Complications	Physical Findings		Aureomycin	
				Proctoscopy	Barium enema	gm. every 6 hr.	days
		yr.					
1	J. W.	4½	Acute brucellosis due to *Br. abortus*	Negative	Negative	0.5 orally* 0.5 orally†	10 10
2	A. C.	4	—	Negative	Negative	0.5 orally	10
3	J. K.	5	Hookworm	Negative	Negative	0.5 orally	18
4	E. N.	6	Chronic colitis and proctitis	Rectal ulcers	Colonic ulcers	0.5 orally	5
5	M. T.	5	Chronic proctitis	Rectal ulcers	Negative	0.5 orally	10
6	B. W.	6	? Hepatitis Cecal granuloma Psychopathic personality	Healed rectal ulcers	Cecum tender, spastic, irregular	0.5 orally	21
7	G. H.	5½	Chronic proctitis	Rectal ulcers	Negative	0.5 orally	10
8	W. B.	4	Cecal granuloma	Negative	Cecum constricted	0.5 orally* 0.5 orally†	17 21
9	L. L.	5	Regional ileitis	Negative	Cecal deformity Terminal ileal mass	0.5 orally 0.1 intravenously	13 6
10	R. B.	8	Cecal granuloma	Negative	Contraction of cecum	0.5 orally	10

*First course.
†Second course.

Results

In vitro studies. Repeated experiments with 2 strains of *E. histolytica* indicated that aureomycin regularly immobilized the trophozoites in the buffered saline overlay of a liver-extract agar culture within twenty-four hours when present in a concentration of 100 microgm. per ml. or more. A concentration of 50 microgm. per ml. produced a significant reduction in the number of motile trophozoites, but a concentration of 25 microgm. per ml. failed to do so. Microscopical examination of these preparations after forty-eight hours' incubation yielded similar results. Furthermore, subcultures of the sediment from the buffered saline overlay to fresh medium of the same composition confirmed the microscopical interpretation; the nonmotile trophozoites proved to be nonviable. Measurements of the pH of various concentrations of the aureomycin in buffered 0.5 per cent saline solution showed only a very slight reduction — certainly not enough to account for the decrease in viable trophozoites. There was, however, an accompanying decline in viable bacteria, which considerably hindered interpretation of the experimental results. It is a well known fact that it is extremely difficult to maintain the viability of *E. histolytica* trophozoites in vitro in the absence of a favorable bacterial flora. Motile bacteria were found to be numerous after twenty-four hours in preparations containing as much as 100 microgm. per ml. of aureomycin. The bacteria were immobilized in concentrations of aureomycin exceeding this amount. Subcultures of the buffered-saline overlay of the experimental tubes (after twenty-four hours) into trypticase broth indicated only a slight reduction in the number of viable bacteria caused by 100 microgm. per ml. of aureomycin and a marked reduction by 500 microgm. per ml. Subcultures of the same tubes onto agar plates revealed that the surviving bacteria were almost all *Pseudomonas aeruginosa*. This might account in part for the decline in viable trophozoites,

since this bacterium regularly produces marked changes in culture media.

In order to circumvent some of these difficulties a second method of study was employed, namely, petrolatum-sealed glass-slide preparations of amebic trophozoites suspended in buffered saline solution containing varying concentrations of aureomycin. In the absence of aureomycin, bacteria and trophozoites remained actively motile in such preparations for at least twenty-four hours. When exposed to large concentrations (500–5000 microgm. per ml.) of aureomycin, all the trophozoites ceased to move within five to fifteen minutes. Most trophozoites quickly ceased to put out pseudopodia, assumed a round contour and entered a precystic stage. Occasionally, however, trophozoites were observed to slow gradually and then suddenly to lyse. The cell wall seemed to rupture and the protoplasm flowed out through the defect. Within a few seconds all remnants of such organisms completely disappeared. Aureomycin in these concentrations stopped bacterial motility in thirty minutes. When lesser amounts of the antibiotic were employed, similar but slower changes were observed. Thus, with 100 microgm. per ml. most trophozoites ceased moving in forty-five minutes although motile bacteria were observed for two hours. Fifty microgm. per ml. inhibited motility of both in two and a half hours. Twenty-five microgm. per ml. had a similar effect in four hours, and 10 microgm. per ml. did not stop the activity of all the trophozoites and bacteria in twenty hours but did so in twenty-four hours.

Identical slide tests were performed with trophozoites of *Endamoeba coli* and *Endolimax nana*. These parasites proved to be more resistant to the in vitro action of aureomycin. A few *Escherichia coli* trophozoites remained motile for two hours in the presence of 500 microgm. per ml. although almost all the bacteria had been immobilized. *E. coli* and *E. nana* trophozoites showed sluggish motion after one and a half hours' exposure to 1000 microgm. per ml.

A few experiments were carried out to compare the effect of emetine hydrochloride and chloramphenicol on *E. histolytica*. A 1:10,000 dilution of emetine immobilized all the trophozoites in twenty-four hours in a buffered saline-solution overlay on liver-extract agar medium. There was no diminution in motility with a 1:50,000 dilution of emetine.

Chloramphenicol in a concentration as high as 2500 microgm. per ml. did not reduce the activity of the parasites under similar conditions. The motile bacterial flora was not detectably reduced by either emetine or chloramphenicol in the concentrations used. However, the method did not allow any quantitative estimate of the number of resistant motile bacteria. With the glass-slide method, 2500 microgm. of chloramphenicol per ml. rendered the bacteria nonmotile in two hours, but the trophozoites remained active for more than three hours.

Clinical studies. To date 20 patients with amebiasis have been treated at this hospital. Nineteen of these patients had chronic amebiasis; one had an acute fulminating infestation. The latter was the only fatal case in the series. All but 2 cases could be traced to service with the United States Armed Forces during World War II, either in the South

TABLE 1 (*Concluded*).

Case No.	Patient	Feces				Results	Follow-up Period
		Before treatment		After treatment			
		findings	*no. of times*	*findings*	*no. of times*		mo.
1	J. W.	Cysts*	3	Negative	22	Well	14
		Trophozoites	3			Second course for brucellosis	
		—†	—	Negative	6		
2	A. C.	Cysts	2	Negative	24	Well	12
		Trophozoites	3				
3	J. K.	Cysts	3	Negative	6	Well	9
4	E. N.	Trophozoites	10	Negative	4	Well	8
5	M. T.	Trophozoites	3	Negative	12	Well	14
				Cysts	4	Cyst passer	
6	B. W.	Trophozoites	6	Negative	2	Temporary improvement	
				Trophozoites	1		
7	G. H.	Trophozoites	3	Negative	9	Well	6
8	W. B.	Trophozoites*	3	Negative	3	Temporary improvement*	2
		Cysts†	2	Negative	4	Well†	1
		Trophozoites	2				
9	L. L.	Cysts	2	Negative	1	Feces negative, but operation necessary for ileitis	
						Well	6
10	R. B.	Negative	8	Negative	7	No diarrhea	
		Trophozoites 3 yr. earlier				?Decrease in cecal deformity	
						Well	3

Pacific or in North Africa. The cases have been divided into 3 categories: chronic amebic dysentery, 10 patients, amebic cyst passers or "carriers," 6 patients and amebic hepatitis or hepatic abscess, 4 patients.

Chronic amebic dysentery. As shown in Table 1, the 10 patients with chronic amebic dysentery admitted symptoms of four to eight years' duration prior to aureomycin therapy. Four of these 10 patients had received earlier treatment with emetine hydrochloride, carbarsone and diiodo-hydroxyquinoline (Diodoquin) followed by temporary improvement. Several of the patients had complications. These included: rectal ulceration in 4, deformity of the descending colon or cecum in 5, regional ileitis in 1, hookworm in 1 and acute brucellosis (*Br. abortus*) in 1. It can be seen that on an average dose of 0.5 gm. of aureomycin by mouth every six hours for ten days the results on the whole were satisfactory. As in the first patient (No. 1 in Table 1), the parasites usually disappeared from the stools within twenty-four hours after the first dose, although in 2 patients forty-eight to seventy-two hours' treatment was required before the parasites disappeared. Repeated examination of purged stools failed to reveal either cysts or trophozoites in 7 of the 10 patients after treatment. These patients were re-examined at intervals; their feces proved to be free of amebae as late as twelve to fourteen months after cessation of treatment. There were 3 exceptions: One patient (No. 5 in Table 1) became a cyst passer (asymptomatic). Another patient

TABLE 2. *Treatment of Human Amebiasis with Aureomycin at Minneapolis Veterans Administration Hospital, 1949: Amebic Cyst Passers.*

Case No.	Patient	Years Since Onset	Physical Findings		Aureomycin		Feces				Results	Follow-up Period
			Proctoscopy	Barium enema	gm. every 6 hr.	days	Before treatment		After treatment			
							findings	no. of times	findings	no. of times		mo.
1	R. K.	5	Negative	Negative	0.5 orally	10	Cysts	2	Negative	4	Feces negative	3
2	L. S.	?	Negative	Negative	0.5 orally	10	Cysts	4	Negative	4	Feces negative	1
3	R. S.	7	Negative	Negative	0.5 orally	10	Cysts	1	Negative	12	Feces negative	11
4	K. S.	5	Negative	Negative	0.5 orally	10	Cysts	2	Negative	7	Feces negative	7
5	H. S.	32	Negative	Negative	0.5 orally	10	Cysts	3	Negative	1	Feces negative	7
6	J. D.	37	Negative	Negative	0.5 orally	10	Cysts	2	Negative	5	Feces negative	6

TABLE 3. *Treatment of Human Amebiasis with Aureomycin at Minneapolis Veterans Administrative Hospital, 1949: Amebic Hepatitis or Hepatic Abscess.*

Case No.	Patient	Duration of Symptoms	Complications	Liver Functions*		Aureomycin	
				Before treatment	After treatment	gm. every 6 hr.	days
1	G. B.	5 yr.	Amebic hepatitis Hepatic cirrhosis Cecal granuloma	BSP 12.5% SB 0, 0.1 CCF 0, 1+ TT 1.0	BSP 5.9%	0.5 orally	11
2	A. S.	7 yr.	Amebic hepatitis	BSP 9.4% SB 0.1, 0.5 CCF 0, ± TT 8.5 $ZnSO_4$ 12	BSP 7.2% SB 0, 0.3 CCF 2+, 2+ TT 7.4 $ZnSO_4$ 15	0.5 orally* 1.0 orally† 0.5 orally‡	10 9 7
3	C. S.	5 yr.	Amebic hepatitis	BSP 18% SB 0.3, 0.5 CCF 0, 0 TT 1.2	BSP 2.2% SB 0, 0.2 CCF 0, 0 TT 8.6	0.25 orally* 0.25 orally†	4 8
			Pneumonia, L.L.L.	$ZnSO_4$ 8.5	$ZnSO_4$ 14.0	0.5 orally‡	4
4	R. H.	1 wk.	Acute fulminating amebic colitis and proctitis Multiple liver abscesses	BSP 13.2% SB 0.1, 0.4 CCF 3+, 4+ TT 3.7 PT 19.5%		0.5 orally 0.05 intravenously	10 3

*First course.
†Second course.
‡Third course.

BSP = bromsulfalein retention 45 min. after 5 mg./kg.
SB = serum bilirubin in mg./100 ml., 1 min. and total.
$ZnSO_4$ = zinc sulfate turbidity, units.
CCF = cephalin cholesterol flocculation, 24 and 48 hours.
TT = thymol turbidity, units.
PT = prothrombin concentration.

(No. 6 in Table 1) improved temporarily, but amebic trophozoites were again found in his feces shortly after aureomycin was discontinued. *Endamoeba gingivalis* was recovered from his gingivae. It was not clear that the trophozoites in his feces were pathogens. A third patient (No. 8 in Table 1) improved temporarily but had recurrent symptoms accompanied by the finding of amebic trophozoites and cysts in his feces shortly after aureomycin was discontinued. A second course of aureomycin was given and the amebae again disappeared.

Symptomatically, the results were equally good. Diarrhea and intestinal cramps ceased within a few hours in most patients. Curiously, some patients noted constipation during treatment with aureomycin, a finding that differed considerably from our general experience with this drug. The improvement in symptoms was lasting in most patients. Seven of the patients have remained asymptomatic for three to fourteen months (average 9.4 months) after the treatment ceased. One patient (No. 6 in Table 1) had recurrent symptoms, which could not be accurately interpreted because of his psychopathic personality. Another patient (No. 8 in Table 1) required 2 treatment courses before his symptoms disappeared. Emetine and diiodohydroxyquinoline (Diodoquin) were given with the second course of aureomycin, because of a relapse after treatment with aureomycin alone. A patient (No. 9 in Table 1) with regional ileitis developed paralytic ileus during aureomycin therapy. Amebae disappeared from his feces, but surgical excision of the involved ileum was necessary. The excised tissue showed no pathologic evidence of amebiasis. Two of the patients who had recurrent symptoms following aureomycin therapy showed evidence of a cecal granuloma, which might have contributed to the therapeutic failure.

There was considerable objective evidence of improvement in this group. Gross and occult blood (as well as amebae) disappeared from the feces. In the 3 cases in which proctoscopy revealed active ulceration prior to therapy, there was almost complete healing at the conclusion of treatment. A patient (No. 4 in Table 1) who showed evidence of ulceration of the mucosa of the descending colon in a barium-enema examination before treatment had a normal mucosal pattern after treatment with aureomycin. Four patients had a deformed cecum prior to treatment. A barium-enema examination was performed in 3 of these patients after aureomycin was given; in each there was somewhat less contraction and irregularity of the cecum, but in none did the cecum appear entirely normal.

Amebic cyst passers ("carriers"). Six patients were placed in this category (Table 2). None of these patients had symptoms or signs of intestinal inflammation when they were treated. However, 5 of the 6 had served in an area where amebiasis was endemic from five to thirty-seven years before they were studied at this hospital. The duration of their "carrier" state is difficult to define because

TABLE 3 (*Concluded*).

CASE No.	PATIENT	FECES				RESULTS
		BEFORE TREATMENT		AFTER TREATMENT		
		findings	*no. of times*	*findings*	*no. of times*	
1	G. B.	Cysts Trophozoites	6 6	Negative	5	Well for 5 mo.
2	A. S.	Cysts* Trophozoites	1 4	Negative Trophozoites Cysts	2 4 1	Improved, but feces positive after 1st course and during 2nd course
		—†	—	Negative	4	Well after emetine
		—‡	—	Negative	4	+ Diodoquin + aureomycin
3	C. S.	—*	—	—	—	Improved but relapsed
		—†	—	—	—	No benefit with 2 more courses
		Cysts‡	1	Negative	16	Recovery with emetine + Diodoquin
4	R. H.	Trophozoites	3			Feces negative, but continued fever Improved with emetine Colon perforated Died

they admitted few or no past intestinal difficulties. Since Minnesota is in an area where amebiasis is infrequent, it seems safe to assume that these patients became infested with amebae while serving in an endemic area.*

Aureomycin was given to all these patients in the standard dose previously cited. Cysts of *E. histolytica* were found in the feces of all the patients before treatment, but there was no evidence of trophozoites. After twenty-four to seventy-two hours' treatment, cysts could no longer be found in the feces. Moreover, no parasites were found in formed or purged stools of any of these patients after treatment. These patients have been studied for an average of six months after treatment. Approximately 5.5 stool specimens per patient have been examined since the aureomycin was discontinued.

Amebic hepatitis or hepatic abscess. There were 4 patients in whom there was definite evidence of hepatic involvement (Table 3). There were 3 patients who appeared to have amebic hepatitis and 1 patient had multiple liver abscesses, presumably due to *E. histolytica.* These cases were of particular interest and hence will be presented in some detail.

Case Reports

Case 1. G. B., a 32-year-old man, developed diarrhea while in New Guinea in 1944. This recurred several times during the next two years. He was then in good health until 1949, when he developed diarrhea, fever, anorexia and pain in the right lower chest radiating to the right shoulder. He had lost 32 pounds. His liver was palpable and tender. Proctoscopic examination indicated no abnormality. A barium-enema examination revealed a constriction of the base of the cecum. His feces contained both trophozoites and cysts of *E. histolytica.* A battery of liver-function tests was performed; only the bromsulfalein retention test was abnormal (Table 3). His recovery, with aureomycin therapy, was uneventful. A barium-enema examination indicated healing of the cecal granuloma. The bromsulfalein retention returned to normal, and parasites disappeared from his feces. A liver biopsy four months later showed an increase in periportal connective tissue and pigment deposition consistent with early cirrhosis. The patient had imbibed alcoholic liquors excessively in 1945 but denied drinking alcoholic beverages since that time.

Case 2. A. S., a 28-year-old man, had had recurrent bouts of diarrhea and epigastric soreness since he served in New Guinea in 1943. He had lost 15 pounds. His liver and cecum were palpable and tender. Proctoscopy and barium-enema examination showed no abnormalities. Liver-function tests showed slight retention of bromsulfalein and abnormal serum flocculation (Table 3). This patient was given 3 successive courses of aureomycin. During the first course he improved, but his feces continued to contain cysts and trophozoites of *E. histolytica* after the drug was discontinued. Trophozoites were found during a second course, in which the dose was increased to 1 gm. by mouth every six hours. A third course was therefore given in conjunction with emetine hydrochloride and diiodo-hydroxyquinoline (Diodoquin). His recovery was uneventful. Liver-function abnormalities and hepatic tenderness persisted until the third treatment course, although his diarrhea ceased during the first period of aureomycin therapy.

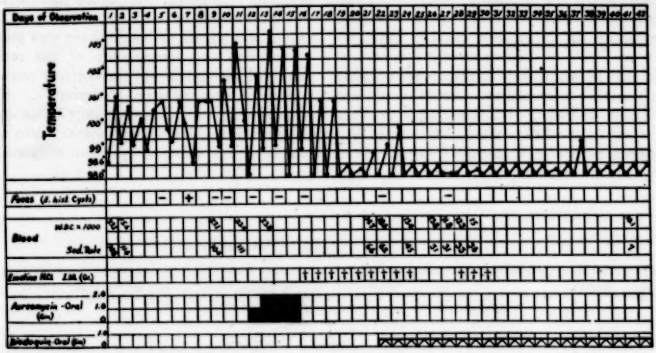

Figure 1. *Case 3 (C. F. S.): Acute Amebic Hepatitis.*

Case 3. C. F. S., a 27-year-old man, had served in the South Pacific in 1944 and 1945 without illness. On February 26, 1949, he noted the onset of nausea, fever, abdominal "tightness" and pain in the right lower chest and back. On March 21 a chest x-ray film taken by his family physician revealed a patchy density in the lower lobe of the left lung. He was hospitalized elsewhere and because of a suspected virus pneumonia was given aureomycin, 0.25 gm. by mouth, every six hours for four days. He became afebrile and felt well enough to go home. However, his fever and abdominal distress recurred in a few days. He was given penicillin and a sulfonamide without improvement. Aureomycin was again advised in a dose of 0.25 gm. orally every six hours for eight days. There was no improvement in his symptoms; the patient was therefore referred to this hospital.

*Probably less than 0.5 per cent of the adult population of the state of Minnesota have cysts or trophozoites of *E. histolytica* in their feces.

On admission (May 12, 1949) he appeared acutely ill. He had lost 25 pounds and his temperature was 101.2°F. (Fig. 1). His lung fields were clear. The liver edge was palpable 4 cm. below the right costal margin and was very tender. There was some tenderness over the splenic flexure of the colon. There was no icterus. His leukocyte count was 27,550, with 84 per cent neutrophils. The erythrocyte sedimentation rate was 108 mm. in one hour. A battery of liver-function tests (Table 3) showed 18 per cent retention of bromsulfalein. Proctoscopic and barium-enema studies indicated no intestinal disease. However, microscopical examination of his feces and seemed critically ill. His abdominal muscles were in moderate spasm and there was tenderness in the epigastric region. His leukocyte count was 25,800, with 83 per cent neutrophils. The erythrocyte sedimentation rate was 77 mm. in one hour. Several of the liver-function tests were abnormal (Table 3). His stools contained *E. histolytica* trophozoites and gross blood. Proctoscopic examination revealed multiple rather deep mucosal ulcers and pustules 3 to 10 mm. in diameter throughout the rectum and sigmoid colon; trophozoites were demonstrated in necrotic material taken

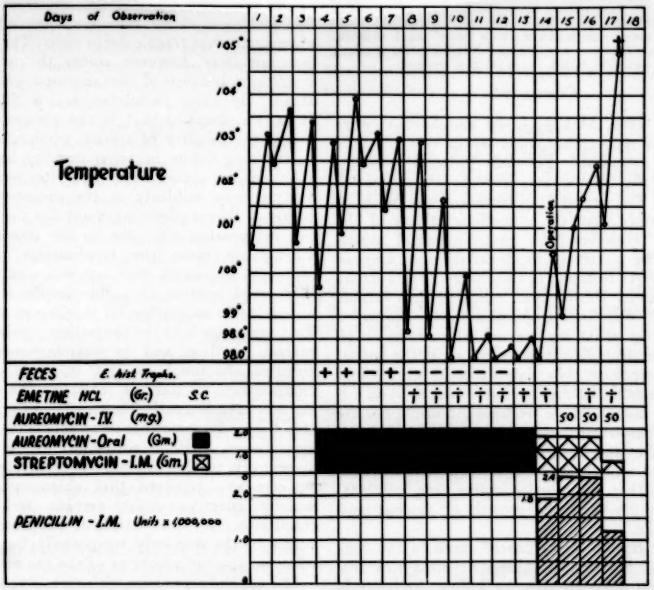

FIGURE 2. *Case 4 (R. H.): Acute Fulminating Amebic Colitis with Hepatic Abscesses.*

disclosed the presence of cysts of *E. histolytica*. A chest x-ray film revealed no pathologic changes. Aureomycin was given in a dose of 0.5 gm. orally every six hours from May 23 through May 26. He continued to have daily chills and fever and marked hepatic tenderness. Parasites could no longer be found in his feces. On May 27 he was placed on a course of emetine hydrochloride and diiodo-hydroxyquinoline (Diodoquin). His temperature promptly subsided to normal and the enlargement and tenderness of his liver rapidly regressed. His recovery was uneventful. It is also of interest that some of the serum-flocculation liver-function tests were abnormal at the conclusion of the third course of aureomycin (Table 3) but all returned to normal after the emetine therapy.

CASE 4. R. H., a 54-year-old man, was employed in a railroad section gang in Minnesota and had not left this state for several years. His illness began suddenly on June 10, 1949, with abdominal cramps, profuse diarrhea, chills, fever and vomiting. He was admitted to this hospital on June 17. His temperature was 103°F. (Fig. 2). He was dehydrated from the ulcers. Because of the dangers involved, a barium-enema examination was not performed.

On June 21 aureomycin was begun, in a dose of 0.5 gm. by mouth every six hours. This was continued for ten days. In spite of the aureomycin therapy he continued to have chills and high fever, accompanied by nausea, vomiting and abdominal pain. His diarrhea lessened somewhat. Stool cultures revealed that the predominant organism was *Ps. aeruginosa*, which proved to be resistant to 50,000 microgm. per ml. of aureomycin. Trophozoites of *E. histolytica* were found in the feces after forty-eight hours' treatment, but none were found in 6 stool specimens examined thereafter. Because of continued fever and abdominal cramps treatment was begun with emetine hydrochloride, 0.065 gm. intramuscularly daily, on June 24. His fever promptly declined but recurred on June 30. At this time he complained of increased abdominal pain; his abdomen was distended, rigid and tympanitic, with few audible bowel sounds. X-ray films revealed free gas in the peritoneal cavity. Penicillin and aureomycin hydrochloride were given intravenously with intramuscular injections of streptomycin. Within a few hours after

the recognition of the signs of a ruptured viscus, a laparotomy was performed under cyclopropane anesthesia. A perforation of the sigmoid colon was closed and the involved segment of the colon was exteriorized. There was evidence of a generalized peritonitis; culture of the abdominal fluid yielded *Ps. aeruginosa*. His immediate postoperative condition was fair. However, his condition gradually became worse, and he died on July 3. An autopsy was performed.* The abdomen contained 2000 ml. of purulent fluid and many fibrinous adhesions. There was an abscess between the liver and the transverse colon, draining into the latter. The liver contained numerous thick-walled abscesses 3 to 6 cm. in diameter containing purulent, necrotic debris from which *Ps. aeruginosa* was isolated by culture. One liver abscess had perforated into the right posterior subphrenic space. The entire colon was involved, with large superficial ulcers that were confluent in many places, leading to a loss of much mucosa. No further perforations were found. Microscopical sections of the colon and liver failed to reveal any amebae.

Comments

In June, 1949, McVay, Laird and Sprunt[6] were the first to report that aureomycin was effective in human amebiasis. Fourteen patients were included in this preliminary report; all responded favorably. The period of observation was too brief to assess more than the immediate effects of the antibiotic. However, the gastrointestinal symptoms of the patients disappeared, and amebae could no longer be found in their feces. The authors cited studies by Hewitt that indicated that various strains of *E. histolytica* trophozoites were destroyed by an overlay of 0.8 mg. per ml. of aureomycin on an egg-yolk alcoholic-extract medium at the end of six hours' exposure. No viable amebae were found after exposure to 0.2 mg. per ml. of aureomycin for forty-eight hours. These workers did not speculate on the mechanism of the amebicidal action of aureomycin. Fuller and Faust[6] tested the activity of the drug against a single strain of *E. histolytica* in vitro. They noted that in a dilution of less than 1:100,000 aureomycin inhibited the growth of amebae and bacteria alike.

Recently Bradin and Hansen[7] came to the conclusion that aureomycin killed *E. histolytica* trophozoites indirectly in vitro by killing the bacteria necessary for maintenance of the proper oxidation-reduction potential in the culture medium. They used a strain of *E. histolytica* grown with a single bacterial species in a liquid liver-proteose-peptone medium buffered at a pH of 6.0 to 6.8. In tubes stoppered with cotton a 1:500,000 dilution of aureomycin hydrochloride killed the amebae within forty-eight hours. However, if the tubes were sealed with petrolatum a dilution of 1:20,000 or less was necessary to kill the amebae. The difference in activity appeared to be due to the fact that sealing the tubes allowed a favorable drop in oxidation-reduction potential (Eh), permitting survival of the amebae in spite of the fact that the bacteria were inhibited. Their conclusion that aureomycin did not act directly against the amebae is difficult to reconcile with some of the observations reported in this paper. It seems significant that Bradin and Hansen did not include direct evidence showing that aureomycin produced bacteriostasis under the conditions of their experiments. They assumed, however, that bacteriostasis by aureomycin prevented a favorable fall in Eh in the presence of air and hence death of the amebae. In the absence of free access to air, the Eh fell and the amebae survived in spite of bacteriostasis. In the latter instance it was apparently assumed that bacteriostasis had occurred.

Our own experiments left no doubt that in a concentration of 50 microgm. per ml. or more aureomycin was amebicidal in vitro. The mechanism was not clear, however, under the usual culture conditions because of the accompanying bacteriostasis. By using petrolatum-sealed slide preparations, we observed that in the presence of aureomycin the motility of amebic trophozoites usually ceased long before bacterial motility had stopped. Furthermore, occasional trophozoites were observed to lyse very suddenly in the presence of motile bacteria. These effects were not due to pH changes but presumably were due to the direct action of aureomycin upon the trophozoites. Oxidation-reduction potentials were not recorded.

It is of interest that chloramphenicol did not appear to be as amebicidal in vitro as aureomycin. This was true both in the saline overlay of liver-extract medium and in petrolatum-sealed slide cultures. As much as 2500 microgm. per ml. of chloramphenicol did not interrupt the motility of the amebae. Recently Thompson and others[8] found this drug to be somewhat more amebicidal in a liquid egg-infusion medium although not so active as aureomycin proved to be in our experiments. These workers also reported that chloramphenicol was equally effective under aerobic and anaerobic conditions. In their hands it suppressed amebic colitis of the dog only temporarily but was more effective against infections of the rat cecum.

Our clinical experience with aureomycin in chronic human amebiasis indicates that it is a very effective agent. Of 10 patients having chronic amebic dysentery, 7 recovered after one course of aureomycin and remained well for three to fourteen months (average, eight months). One so-called "failure" became asymptomatic and had demonstrable healing of rectal ulcers but had *E. histolytica* cysts in his feces after treatment. A second "failure" was difficult to analyze because of an *E. gingivalis* infestation and marked personality defects. The third "failure" might well have been due to the presence of a cecal granuloma. These results compare favorably with other reports in the literature. McVay and his co-workers[6] stated that they had treated 14 patients successfully with no recurrence of symptoms. Most[9] found that 7 out of 8 patients given 20 gm. of aureomycin orally in ten days remained free of *E. histolytica* after treatment. A patient with amebic dysentery was given aureomycin by

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MacDonald[10] and quickly recovered. The most extensive series reported was that of Hughes.[11] The latter gave his patients 7 gm. of aureomycin over a period of four to seven days. Of 38 patients treated in this manner, 27, or 71 per cent, apparently were cured. However, his patients often had only one follow-up parasitologic examination, and that only two weeks after treatment. Anderson and Anderson[12] attempted to confirm the efficacy of aureomycin by experiments in monkeys. They were able to rid the feces of amebae only temporarily in a small group of animals. No reports have appeared concerning the treatment of human cyst passers or "carriers." Our results in 6 patients in this category have been uniformly good; negative stool examinations for ova and parasites were attained by every patient (average follow-up, six months).

The effects of treatment have not been so salutary in the presence of hepatic complications, despite the early optimism of McVay and his co-workers.[5] Hughes[11] cited a good response to aureomycin in a patient with apparently mild hepatitis complicating amebic colitis. He went on to state: "However, I have seen a severe amebic liver abscess which failed to respond to heavy and prolonged doses of aureomycin but which resolved promptly with emetine hydrochloride." In the present series there were 3 cases with amebic hepatitis and 1 with hepatic abscesses. Only 1 of the 3 patients having hepatitis became asymptomatic and free of amebae upon stool examination after a single course of aureomycin. The patient who had liver abscesses showed no symptomatic benefit from aureomycin, although amebae disappeared from his feces. At the present time it appears that aureomycin should not be used alone in the presence of hepatic amebiasis but should be supplemented by emetine hydrochloride or chloroquine, or both.

Nonetheless, aureomycin appears to be a useful adjunct in the treatment of amebic dysentery and of amebic cyst passers, particularly in cases that have not been cured by the usual amebicidal drugs. The lack of serious toxicity is a great advantage. Of the 20 patients reported here, 11 had no side-effects while taking aureomycin. Three patients complained of soft, frequent stools, 3 had nausea and vomiting and 2 stated that they had some epigastric distress, which was relieved by giving the drug with milk. Another patient had recurrent urticaria, which could not be definitely attributed to aureomycin. In no case were the side-effects so severe as to interrupt the treatment. Although the standard dose used in this series was 0.5 gm. by mouth every six hours for ten days, it is not certain that this is the optimum dose.

In the course of these studies it was noted that several of the patients had parasites other than *E. histolytica* in their feces. Five patients had trophozoites or ova of *E. coli* or both before aureomycin was given, but these had been eliminated by the treatment in 4 cases. *E. nana* were observed to disappear from the stools of all of 4 patients in whom they were found prior to treatment. *Iodamoeba bütschlii* could no longer be seen in the stools of 2 patients after treatment, although they had been heavily infested earlier. These observations were somewhat surprising, since we found *E. coli* and *E. nana* quite resistant to aureomycin in vitro. It seems pertinent to mention the fact that we have treated 3 cases of hookworm (*Ancylostoma duodenale*) disease, 3 patients with trichomonas vaginitis and 2 patients having *Trichomonas hominis* in their feces by oral administration of aureomycin, with no benefit.

Summary

Aureomycin hydrochloride killed *E. histolytica* trophozoites in vitro in concentrations as low as 50 microgm. per ml. Although this effect was undoubtedly in part the consequence of an alteration of bacterial flora, there was evidence that aureomycin also directly attacked the amebae.

Aureomycin was given to 20 patients with amebiasis, in 19 of whom the disease was chronic. Seven of 10 patients who had chronic amebic dysentery recovered.

All of 6 amebic cyst passers were "cured" by one course of aureomycin.

Only 1 of 4 patients with hepatic amebiasis recovered on one course of aureomycin. Patients having amebic hepatitis or liver abscess should receive emetine hydrochloride or chloroquine, or both.

No serious toxic effects of the drug were noted, although it caused minor gastrointestinal disturbances in several patients.

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CARCINOMA OF THE BLADDER

An Evaluation of Total Cystectomy and Other Methods of Treatment*

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RECENT years have seen an increasing tendency to treat cancer of the bladder by radical methods. The present seems to be the time to evaluate our long-term results of total cystectomy and to determine whether the removal of the diseased bladder has resulted in a significantly higher long-term survival rate than have other less formidable procedures. In particular, the indications for total cystectomy seem to require clarification.

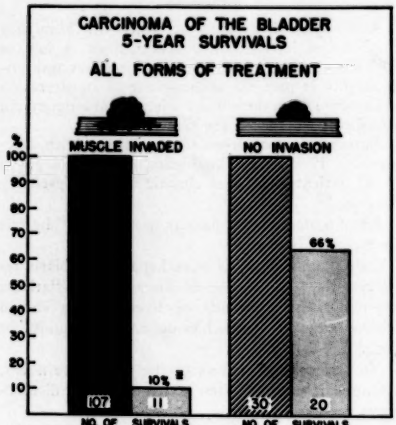

FIGURE 1.

From 1934 to 1950, 103 total cystectomies for cancer of the bladder were performed at the Massachusetts General Hospital. The results up to the present time are known in all these cases. Seventeen of these patients died in the hospital — a postoperative mortality of about 17 per cent. Sixty-three, or 73 per cent, of the 86 survivors have died since operation, 54 from cancer and most of the others from sepsis or uremia. Twenty-three, or about 26 per cent, are alive, 2 with recurrent disease. Since some of these patients have been operated on in the past two years, their future is uncertain and these cases are of little statistical value.

In the ten-year period from 1934 to 1944, total cystectomies were performed on 31 patients. The postoperative mortality during these years was 26 per cent. Only 1 patient of this group is alive. The other 23 patients who survived operation died approximately 16 months after leaving the hospital. Most of these deaths were due to cancer, uremia or infection.

During the five-year period of 1944 to 1949, 60 total cystectomies were performed. Postoperative mortality during these years of added experience and improved methods of controlling infection and blood replacement was 10 per cent. This was a considerable improvement over previous years. Thirty-seven of the 54 survivors, or about 68 per cent, have died approximately fifteen months since operation. Twenty-five died of cancer. The others died of uremia, sepsis, circulatory disease or unknown causes. Seventeen are alive, although 2 have recurrent disease. Twenty-five per cent of these 60 patients, therefore, survived operation and are now living without evident disease. Since 2 patients developed bony metastases five and a half years after operation, the long-term survival rate for these patients will surely be less than 25 per cent.

TABLE 1. *Tumors with Muscle Invasion.*

	No. of Patients	Tumor Grade		Size of Tumor		Mean Age
		II	III	1-3 cm.	3 cm. or over	
		%	%	%	%	yr.
Cystectomy.....	25	24	76	24	76	60
No cystectomy..	82	19.5	80.5	25.6	74.4	63

In trying to ascertain why some patients did well after operation and others did poorly, and in an attempt to clarify the indications for total cystectomy, 700 cases of carcinoma of the bladder treated at the Massachusetts General Hospital from 1934 to 1949 were studied. A review of the microscopical characteristics of these neoplasms suggested that penetration into the bladder muscle might have more significance than the size, grade or location of the tumor or whether it was papillary or nonpapillary. Either papillary or nonpapillary tumors

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can invade the muscle and be termed infiltrating. Jewett* has regarded invasion of the underlying muscle as an important feature of bladder tumors. Our own studies suggest that on this fact can be based more intelligent treatment and more accurate prognosis of cancer of the bladder.

Only those tumors were studied that provided sufficient microscopical material to show whether or not muscle invasion was present. The tumors of patients who had died in the hospital or who could not be followed were omitted. Clinical evidence of invasion was considered inaccurate, since the fibrosis that accompanies some neoplasms may suggest invasion. One hundred and thirty-seven tumors with adequate pathological and follow-up data were available for study. Although this was a small group of tumors, it formed a sound basis for study, since the tissue had been secured by total cystectomy, segmental resection or deep biopsy. (Biopsy specimens from the periphery of a tumor

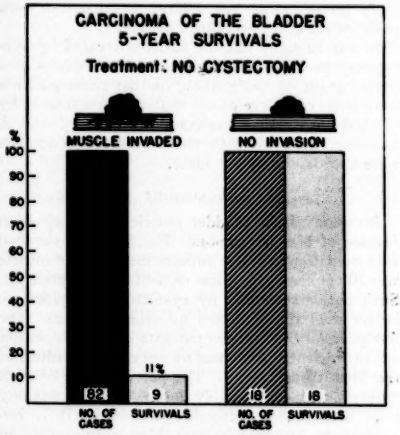

FIGURE 2.

may be misleading and may yield no information about tumor penetration.) This selection also eliminated the small papillary growths limited to the surface that may be satisfactorily treated by fulguration. Thirty-seven cases of total cystectomy met the requirements for inclusion in this study. Other tumors were treated by local destruction or segmental resection.

One hundred and seven tumors invaded the bladder muscle. From all forms of treatment — local destruction, segmental resection and total cystectomy — the five-year survivals were about 10 per cent. Two of these patients developed bony metastases in five and a half years and are now dead. Thirty tumors showed no microscopical evidence of muscle invasion. Twenty, or 66 per cent,

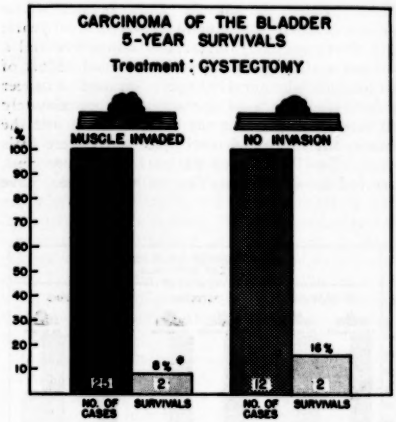

FIGURE 3.

survived the five-year period with no evidence of tumor when all forms of treatment had been employed.

For an evaluation of different methods of treating these tumors, other forms of treatment than total cystectomy were compared with regard to when the

TABLE 2. *Tumors with No Muscle Invasion.*

	No. of Patients	Tumor Grade		Size of Tumor		Mean Age
		II	III	1-3 cm.	3 cm. or over	
		%	%	%	%	yr.
Cystectomy	12	8.3	91.7	66.6	33.4	57.3
No cystectomy .	18	6.2	93.8	74	25	62

tumors did and did not invade the bladder muscle. Eighty-two tumors that invaded the muscle were treated by methods other than cystectomy. Nine, or 11 per cent, of these patients whose tumors invaded the muscle survived five or more years. Eighteen tumors that did not invade the muscle were treated by methods other than cystectomy. All these patients were alive and well after five years. These figures illustrate the difference in curability of tumors that invade the bladder muscle and tumors that

*Jewett, H. J., and Strong, G. H. Infiltrating carcinoma of bladder: relation of depth of penetration of bladder wall to incidence of local extension and metastases. *J. Urol.* 55:366-372, 1946.

do not invade the muscle. Segmental resection or local destruction obviously was not sufficient to control most of the tumors that invaded the muscle. When the muscle was not invaded, however, these measures were adequate.

Total cystectomy was employed in 37 cases concerning which we have adequate histologic and follow-up data. In twenty-five of these cases the tumor invaded the muscle. Only 2 cases whose tumors invaded the muscle survived five years; both developed bony metastases about five and a half years after operation and have died. Most of the patients who survived operation died of cancer or from the effects of operation in approximately ten months. When the tumors did not invade the muscle, the results of total cystectomy were little better. Two of 12 such patients, or 16 per cent, survived for five years. Ten, or 84 per cent, have

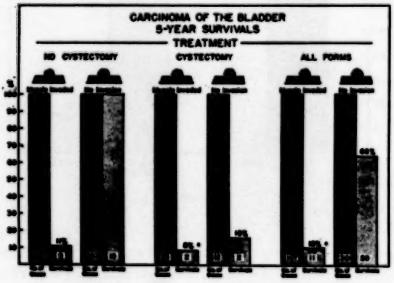

FIGURE 4.

died. It was believed that many of these deaths were the result of operation, since disturbed body chemistry, infection and failing renal function were the chief causes of death. Five of the deaths were caused by uremia. Other deaths were due to cerebral accidents or uncertain causes. As far as could be determined, no patients whose tumors did not invade the muscle died of cancer.

It seems, judging by these figures, that invasion of the underlying muscle in a bladder tumor implies a poor prognosis. Regardless of the method of treatment — local destruction, segmental resection or total cystectomy — few such patients survived a five-year period. When the muscle was not invaded the situation was different. Most such tumors were satisfactorily treated by methods other than total cystectomy. When total cystectomy was used for tumors that did not invade the muscle, the five-year survival rate was considerably lower than when less radical methods were used. Since there is no evidence that the patients with noninvasive tumors died of cancer after cystectomy, it must be assumed that many of them died from the effects of operation: uremia, sepsis and failing renal function.

Involvement of the regional lymph nodes by carcinoma of the bladder requires careful consideration. Since there are no lymphatics in the mucosa of the bladder, tumor invasion of the deeper layers should increase the tendency to lymphatic spread. There is no evidence that any tumor, in our cases, that did not penetrate the muscle had spread to the regional lymph nodes. Forty per cent of 15 tumors that did invade the muscle and that were treated by cystectomy and surgical removal of the pelvic lymph nodes involved the regional lymph nodes. If the bladder muscle is invaded by tumor the regional lymph nodes should be removed, if possible, regardless of the method used to remove the primary tumor. Otherwise a large proportion of such patients are given no chance of cure.

It was thought the the patients treated by cystectomy perhaps had larger tumors or tumors of a higher grade of malignancy, or that these patients were in an older age group than patients treated by methods other than cystectomy. Tables 1 and 2, however, show that in these respects conditions were approximately the same.

Conclusions

Invasion of the bladder muscle is an important feature of bladder tumors. The five-year survival rate of patients whose tumors invaded the muscle was 10 per cent, regardless of the form of treatment. Such patients treated by cystectomy survived no longer than those treated by other methods. The five-year survival rate of patients whose tumors did not invade the muscle was 64 per cent, regardless of the form of treatment. The survival rate of such patients was considerably lower after cystectomy than when other methods were used. It is important to secure adequate biopsy specimens to determine whether or not the tumor invades the muscle. If the muscle is not invaded, the tumors should be treated whenever possible by methods other than cystectomy. Tumors that invade the muscle have a poor prognosis with any present method of treatment. The high incidence of lymph-node involvement in tumors that invade the muscle shows that unless these lymph nodes can be removed the death rate from cancer will continue to be high.

THE IMPORTANCE OF A HIGH-PITCHED SQUEAKING SYSTOLIC MURMUR IN THE DIAGNOSIS OF AORTIC STENOSIS AND CALCIFICATION OF THE AORTIC VALVE*

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THE primary purpose of this report is to emphasize the relation of a high-pitched "squeaking" or "musical" systolic murmur to aortic stenosis and calcification of the aortic valve. This is not so widely appreciated as it should be, for we have found that a high-pitched musical systolic murmur is more often attributed to obscure causes than to aortic valvular disease. Some writers[1, 2] even suggest that musical murmurs are not significant.

It is rather surprising that this frequent and almost specific tonal quality of the murmur of aortic stenosis receives little emphasis in clinical teaching. No mention of it is found in many modern cardiac texts and in most of the recent literature on aortic stenosis. To our knowledge there is only occasional brief mention of the significance of this murmur in the literature of the twentieth century.[3-11] Yet Stokes,[12] writing in 1854, and some of the other older writers[13-18] knew of the association of this high-pitched systolic bruit with aortic stenosis and described it picturesquely as resembling the "squeak of a mouse or guinea pig" or the "high note of a fiddle." Osler[3] was aware of it and characterized it as "high pitched, whistling and musical." In our experience this murmur is to be confused only with a brief and probably extracardiac systolic squeak heard in the left precordium of young persons with otherwise normal hearts.

The squeaky systolic murmur of aortic stenosis usually is loudest in the apical region, left sternal border or lower precordium and thus diverts attention from the aortic valve. Always associated with this musical sound, however, is a rough, although perhaps very faint, systolic murmur, with or without a high-pitched quality, heard in the right second interspace. The basal rough or rasping murmur of "classical" aortic stenosis is so often very loud that it should be emphasized that the rough quality may be present even when the murmur is quite faint and at times barely audible. If the diagnosis of aortic stenosis is to be made early, the quality is more helpful than the intensity in the determination of the significance of a basal systolic murmur. Early in the disease, or in an emphysematous or thick-walled chest, it may be so faint that only careful search will reveal its presence. Thus, a precordial or apical systolic murmur with a high-pitched component calls for painstaking search for a basal murmur with a rough quality; when this is found the diagnosis of aortic stenosis may be made.

In addition to this peculiar quality of the murmur of aortic stenosis, it should be noted that the point of maximum intensity often is not in the aortic area. Marked prominence of the murmur at or near the apex is ignored in many discussions of aortic stenosis and is emphasized in relatively few. Thus, it is not surprising that patients originally suspected of having mitral regurgitation are later revealed as having aortic stenosis instead. When a predominantly apical systolic murmur, even without a high-pitched quality, is present in older persons careful auscultation of the aortic area will often reveal a faint, rough systolic murmur. With such findings a diagnosis of aortic stenosis must be seriously considered.

Judging from our observations, the earliest finding in aortic stenosis is a relatively faint systolic murmur with a definitely harsh quality, with or without a terminal high-pitched component localized in the second right interspace. This murmur is easily missed and when heard is frequently attributed to a sclerotic or dilated aorta or dismissed as inconsequential. Thus, in persons with "classical" aortic stenosis it is not unusual to find that a murmur has been heard ten or twenty years previously. Occasionally such a murmur has been found during a life-insurance or army-induction[19] examination and its significance discounted. Aortic stenosis is usually a slowly progressive disease that even after fifteen or twenty years may show a minimal number of the "classic" signs and relatively little cardiac functional impairment. The slowly progressive nature of the disease process and the long period that may be required for the transition from a faint to an unmistakably significant murmur are, with the other signs of the disease, well recognized in recent writings.

After observing and following a large number of cases of aortic stenosis we are satisfied that a normal or even accentuated aortic second sound, a wide pulse pressure, a normal electrocardiogram, a normal heart size and even normal configuration on x-ray examination are not infrequent findings in aortic stenosis. Fluoroscopic examination with attention directed toward the aortic valve may be very important, however, by demonstrating valvular calcification and thereby confirming the diagnosis. Painstaking search may reveal the presence of a basal thrill even when there are no findings of aortic stenosis other than the murmurs mentioned

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above. This discovery adds weighty confirmation, of course, but is by no means necessary for a diagnosis. We suspect that an emphysematous thorax or a thick chest wall masks many a thrill.

Aortic stenosis has been found to be a surprisingly common cardiac condition in adults over 50 years of age. We are certain that if careful attention is paid to auscultation of the second right interspace and to the tonal qualities of any systolic murmur present in that area, no matter how faint, the disease can be diagnosed or at least suspected much earlier and more frequently than is generally the case at present.

Case Reports

Case 1. A 76-year-old woman was first seen in October, 1949, because of a ten-month history of increasing dyspnea, orthopnea and angina pectoris. Examination revealed moderately severe congestive heart failure. The heart seemed moderately enlarged and there was a Grade III rough systolic murmur over the precordium, faintly heard in the right 2nd interspace. In a localized area somewhat above the apical impulse the murmur had a high-pitched squeaky quality. No thrill was felt. The aortic second sound was accentuated. The blood pressure was 210/130.

X-ray examination showed a generally enlarged heart. The electrocardiogram revealed changes consistent with left-ventricular hypertrophy.

After two months of steadily increasing failure, she died of acute pulmonary edema a few minutes after her second admission.

Autopsy revealed a heart weighing 615 gm. and marked coronary arteriosclerosis. The aortic leaflets were flexible and no calcium was seen, but the valves were fused along adjacent cusps. The mitral valve was normal.

Comment. The squeaking quality in a predominantly apical murmur led to a diagnosis of aortic stenosis in addition to coronary and hypertensive heart disease. The latter might have been the only diagnosis unless one appreciated the significance of the squeaking quality of the murmur.

Case 2. A 67-year-old hospitalized woman was seen in consultation because of a sudden acute attack of dyspnea during the preceding night. Her only other cardiac symptom was mild exertional dyspnea for two months. Her heart had been considered sound at previous examinations.

Nothing abnormal was heard on cardiac auscultation at the first examination, but subsequent examinations revealed a barely audible apical systolic murmur with a terminal high-pitched component. Careful auscultation at the 2nd right interspace revealed an extremely faint but rough systolic murmur. No thrill was felt. The aortic second sound was normal. The blood pressure was 160/80.

X-ray examination of the heart revealed no definite abnormality in its size or shape. The initial electrocardiogram revealed right-bundle-branch block and was suggestive of acute subendocardial infarction. The latter could not be definitely established by serial electrocardiograms.

After 3 weeks of improvement she suddenly collapsed, and died within an hour. An electrocardiogram made during this period confirmed a diagnosis of acute anterior myocardial infarction.

Autopsy revealed a heart weighing 410 gm. There was recent myocardial infarction and small calcium deposits along the aortic ring above the sinuses of Valsalva. Aside from thickening and opacity of one leaflet, the mitral valve was normal.

Comment. In this case the murmur was so faint that it was missed on the first examination. It was discovered only on re-examination; because of the high-pitched component in the apical murmur a diagnosis of aortic stenosis was made. In view of the post-mortem findings the presence of functionally important aortic stenosis might be questioned, but it seems fairly certain that the slight calcification of the aortic valves accounted for the cardiac auscultatory findings. It is probable that had this woman lived another decade the disease would have progressed and more clear-cut signs of aortic stenosis would have appeared.

Case 3. A 46-year-old woman was first seen in 1940 with symptoms of neurocirculatory asthenia. The only abnormal findings on physical examination were a slight basal systolic murmur and a blood pressure of 170/105.

X-ray examination and an electrocardiogram were normal.

At the next examination, in 1946, the basal systolic murmur was classified as Grade III. Fluoroscopy revealed blunting of the left ventricle; the electrocardiogram demonstrated left-ventricular hypertrophy.

At subsequent semiannual visits it was noted that the basal murmur became steadily more prominent. At the last visit in June, 1949, the basal systolic murmur was classified as Grade IV and was transmitted all over the precordium; a basal systolic thrill was noted. The aortic second sound was louder than the pulmonic second sound. The blood pressure was 170/95. The electrocardiogram remained unchanged. On fluoroscopy slight left-ventricular enlargement was suspected.

Comment. This case illustrates the importance of faint basal systolic murmurs in the early diagnosis of aortic stenosis. Although no note was made of the quality of the murmur at the first examination, we suspect that even when the murmur was faint it had a rough quality and that aortic stenosis might have been suspected in 1940.

Case 4. A 79-year-old man was admitted to the hospital because of a fractured hip. He had had 3 syncopal attacks and many minor dizzy spells during the preceding seven months. There were no other significant cardiac symptoms.

On cardiac auscultation a Grade III rough apical systolic murmur was heard, transmitted faintly over the precordium. Careful auscultation of the base revealed a rough Grade I systolic murmur with a high-pitched component in the 2nd and 3rd right interspaces. The aortic second sound was louder than the pulmonic second sound. No thrill was felt. The blood pressure was 190/80.

A portable x-ray film of the chest showed no definite cardiac abnormality. The electrocardiogram revealed right-bundle-branch block.

At autopsy on the 19th hospital day death was attributed to multiple pulmonary emboli. The heart weighed 426 gm. In the aortic leaflets were found considerable deposits of calcium, which could be broken like eggshells. The mitral valve was normal aside from slight thickening.

Comment. This case illustrates the importance of careful auscultation of the base in the presence of a loud apical murmur as well as the relation of a high-pitched quality of the systolic murmur in calcific aortic valvular disease.

Case 5. An 80-year-old man was admitted in 1947 after one year of increasing breathlessness and edema. There was a high-pitched, rasping Grade II apical systolic murmur, with similar findings in the aortic area. The blood pressure was 190/70.

X-ray examination revealed marked cardiac enlargement. The electrocardiogram was consistent with healed anterior myocardial infarction.

When he was readmitted in January, 1950, no murmurs were heard, but later a faint, harsh Grade I systolic murmur was found in the right 1st and 2nd interspaces. No apical murmur was present. The aortic second sound was diminished. No thrill could be felt. The blood pressure was 110/70.

A visiting cardiac consultant would not accept the diagnosis of aortic stenosis, but fluoroscopy later demonstrated dancing calcifications in the region of the aortic valve.

Comment. This case demonstrates the presence of calcific aortic valvular disease with a relatively faint but harsh systolic murmur localized in the right side of the base of the heart.

CASE 6. A 68-year-old woman with mild congestive heart failure and auricular fibrillation was found to have a Grade II apical systolic murmur, but its peculiar whistling quality directed attention to the right 2nd interspace, where there was a faint but rough Grade I systolic murmur. When she sat up and held her breath in expiration the murmur was found to be Grade II at the base and less loud at the apex. The aortic second sound was louder than the pulmonic second sound. No thrill could be felt. The blood pressure was 160/80.

X-ray examination showed moderate left-ventricular enlargement. The electrocardiogram was consistent with healed anteroseptal myocardial infarction.

Fluoroscopy demonstrated definite calcification of the aortic valve.

Comment. The whistling quality of a rather faint apical systolic murmur was again the sign of aortic stenosis; fluoroscopy confirmed the diagnosis of calcific aortic valvular disease.

SUMMARY

The importance of a high-pitched squeaking or whistling quality in any systolic murmur is emphasized as a diagnostic sign of aortic stenosis or calcification of the aortic valve.

In the diagnosis of aortic stenosis the rough quality of the basal systolic murmur is more important than the intensity. Unless this fact is recognized a faint basal systolic murmur may be considered inconsequential and aortic valvular disease may thus be overlooked.

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RICKETTSIALPOX IN BOSTON*

Report of a Case

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UNTIL the appearance in 1950 of reports[1, 2] of rickettsialpox in Boston, naturally occurring human cases of the disease had been recognized only in the metropolitan area of New York City. The Boston cases represented in one instance a laboratory infection and in the other a case acquired by natural means in the patient's usual environment. The present report concerns the second naturally occurring case of rickettsialpox diagnosed in Massachusetts.

CASE REPORT

A 46-year-old housewife was admitted to the Boston City Hospital on August 26, 1950, complaining of severe headache and fever of three days' duration. She had apparently been in good health until August 21, at which time she noted the presence of a small vesicle at the base of her right thumb. This vesicle underwent desiccation, and a black crust developed during the next few days. On August 22 there was tenderness in her right axilla, but no red streaks were noted. On August 23, she experienced a severe frontal headache that persisted for several days and was not relieved by aspirin. Malaise, nausea, weakness and fever appeared on August 24. Her oral temperature was 103°F. at this time. She received one injection of 400,000 units of aqueous procaine penicillin without apparent effect on fever or symptoms. An eruption over the thorax and abdomen was first observed on August 27. She entered the hospital on August 26, five days after the appearance of the primary lesion and three days after onset of fever.

The patient had had a tonsillectomy in childhood, an appendectomy in 1916 and a hysterectomy in 1939. She denied all previous communicable diseases other than pertussis at the age of 10. There had been no known recent exposure to contagious disease, and she had not been outside Boston and its immediate vicinity during the preceding two years. She had never been vaccinated against a rickettsial disease. She had never been to Cape Cod, and her last visit to New York City had been in 1946. Mice had been noted frequently in her dwelling, which was located in a crowded and densely populated section of Boston, 1.5 miles from the site where *Rickettsia akari* had been found in mice.[3] During the three weeks prior to the onset of illness, she had not visited that locale of infection. The patient gave no definite history

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of attack by bloodsucking arthropods. The family history was noncontributory.

Physical examination revealed a thin, middle-aged woman suffering from severe frontal headache and malaise. The oral temperature was 103°F., the pulse 96 and the blood pressure 110/70. On the dorsal surface of the right thenar eminence there was an area of induration and erythema with a central black crust, the entire lesion measuring 2 cm. in diameter. A tender, nonfluctuant lymph node about 2.5 cm. in diameter was palpable in the right axilla. There were also several bilateral shotty, nontender inguinal and cervical nodes. Examination of the eyes, ears, nose and throat was negative. There was no tenderness over the sinuses, which transilluminated well. The neck was limber; the trachea was in the midline. Examination of heart and lungs was within normal limits. The abdomen was negative except for well-healed operative scars. A few varicosities were noted in the lower extremities. Neurologic examination was negative. On August 27 there appeared an irregularly scattered, discrete, slightly erythematous maculopapular eruption over the chest, abdomen and back. No large vesicles were seen, but several of the papules were surmounted by opaque areas of pin-point size.

The white-cell count on admission was 8300, with 43 per cent neutrophils. Repeated white-cell counts remained at about this level. The hemoglobin was 12 gm. per 100 cc.

TABLE 1. *Results of Complement-Fixation Tests with Rickettsialpox and Rocky Mountain Spotted Fever Antigens.*

SERIAL SAMPLE	DATE BLOOD DRAWN	DAY AFTER LESION FIRST NOTICED	COMPLEMENT FIXATION*	
			Rickettsialpox	*Rocky Mountain Spotted Fever*
1	August 26	5	0	0
2	August 28	7	0	0
3	August 30	9	20	0
4	September 6	16	160	80
5	September 11	21	320	80

*The figures in these columns are the reciprocals of the serum dilutions to which antigen and complement were added. Lederle's commercial M.K. antigen, Lot No. 2625-15, was used in a constant dilution of 1:8. The tests were performed by Miss Avis H. Ofstrock, in the Department of Microbiology.

Several urinalyses were within normal limits. The blood urea nitrogen was 13 mg. per 100 cc. The corrected sedimentation rate was 20. Stools were guaiac negative. Nose and throat cultures produced only alpha-hemolytic streptococcus, *Neisseria flavescens* and *Staphylococcus albus*. X-ray films of the chest and paranasal sinuses revealed no disease. Two tests for heterophil antibodies on serums taken during the acute phase and in convalescence were negative. Serums failed to agglutinate Proteus OX-19 in the Weil–Felix reaction; agglutination tests for tularemia and brucellosis were negative. Blood cultures were sterile, and stool cultures revealed no pathogenic intestinal bacteria. The results of the complement-fixation tests with rickettsialpox antigen are shown in Table 1.

Recovery was uneventful, and the temperature returned to a normal level by August 30, the duration of fever being six days. The malaise and other symptoms also disappeared as the fever subsided. The rash faded in four days without residual scarring, but the primary lesion regressed more slowly, traces of it still being evident at the time of discharge. No antibiotic or chemotherapeutic agents were administered after hospital admission, treatment being entirely symptomatic. The patient was discharged on September 8, 1950, after fourteen days of hospitalization.

DISCUSSION

The epidemiology and the clinical features of rickettsialpox have been summarized by previous investigators.[1, 2] The present case fits the typical clinical and laboratory picture in every detail. The incubation period of this disease is not well established, but it is considered to be about nine or ten days. There is no special age or sex predilection. In most patients, a primary painless cutaneous lesion can be readily identified at the site of inoculation by the arthropod vector. It usually consists of an area of erythema and induration from 1.0 to 2.5 cm. in diameter. This lesion in an early stage has a central vesicle containing cloudy fluid. It soon ruptures and undergoes desiccation, resulting in a black crust. At this stage it resembles the lesion of primary vaccinia. Our patient exhibited such a lesion on the dorsal surface of her right thenar eminence. As in nearly all reported cases, this patient showed enlargement and tenderness of the lymph nodes draining the area of the primary lesion, without evidence of lymphangitis. The chief constitutional symptoms of fever, headache and malaise usually arise two to seven days after appearance of the primary cutaneous lesion, and the temperature may range from 100.2 to 105.6°F. before declining to normal by lysis after a week.[3] In the present case, systemic symptoms were noted three days after the primary lesion was detected, and normal temperature was achieved after six days of fever, the highest recorded level reaching 103°F. Severe frontal headache, described by Rose[3] as an outstanding feature of this illness, was one of our patient's chief complaints. The cutaneous eruption in the majority of cases appeared within ninety-six hours after the onset of the febrile period.[3-5] In our case, the rash appeared on the fourth day after fever was first noted. The individual lesions may vary considerably in their appearance but most frequently appear as discrete, erythematous maculopapules distributed over the body surfaces. Occasionally this eruption may be so sparse or so faint as to be almost inapparent. Vesiculation of some degree is usually noted. In many cases the vesicles may appear as pin-point areas at the summits of papules. This latter type was exhibited by our case.

The routine laboratory tests regularly fail to detect anything of note, other than a fairly high incidence of moderate leukopenia during the acute phase of illness. The white-cell count is often within normal limits, however, as in this case. During both the acute and convalescent phases of our patient's illness, tests for heterophil antibody were negative, which is the usual finding in rickettsialpox. Among the rickettsial infections, Q fever and rickettsialpox give negative Weil–Felix reactions,[3] as was true in our case.

Serologic methods have been devised for the precise diagnosis of rickettsial diseases. The test most widely used is the complement-fixation reaction, in which serum is tested against antigens prepared from rickettsiae grown in the yolk sacs of chick embryos. The demonstration of the appearance of antibody or of a significant rise in

antibody titer in the convalescent serum establishes the diagnosis. It may be seen in Table 1 that the serum-dilution titer in our case rose from 0 during the acute phase of illness to a level of 1:320 during convalescence, three weeks after appearance of the primary cutaneous lesion and nineteen days after onset of fever. The degree of cross-reaction observed with Rocky Mountain spotted fever antigen is the rule in serums of patients as well as of experimental animals in convalescence from infection with *R. akari*.

Summary

The second naturally occurring case of rickettsialpox diagnosed in Massachusetts is described.

The diagnosis was established by the clinical and laboratory findings, including a significantly elevated complement-fixation titer.

The patient recovered promptly without specific treatment.

This case probably indicates a second focus of natural infection within the city of Boston.

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FIFTY YEARS OF MEDICAL PROGRESS

MEDICINE AS A SCIENCE: MICROBIOLOGY

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THE late years of the previous century witnessed the rise of modern bacteriology and the inception of immunology. The greatest progress in these fields, however, has taken place in the first half of the present century. Notable advances have been made in our knowledge of the physiologic, chemical and antigenic characteristics of pathogenic micro-organisms and of their etiologic relationship to infectious diseases. Immunology has attained its full stature as an associated science. Antibiotics, other chemotherapeutic agents, antiserums, toxoids and vaccines have revolutionized treatment and prophylaxis. These rapid advances have introduced new concepts in the therapy and prevention of infectious diseases and in medical teaching.

The study of the etiologic agents of infectious diseases is no longer merely bacteriology but now includes the broad field of microbiology. In general, microbiology is the study of organisms that are of microscopic or submicroscopic size during their larval or adult existence. In this paper its scope is restricted to the causative agents of disease among the bacteria, fungi, rickettsiae, viruses and protozoa. Likewise, the limitations of space permit only the presentation of certain accomplishments among the numerous developments that have taken place in medical microbiology.

Medical Microbiology

The science of microbiology is a fundamental part of medicine; problems of infection, immunity and chemotherapy of infectious diseases are often solved by a knowledge of the biologic activities of the etiologic agent and its host-parasite relation. The advances in microbiology during the past fifty years have been concerned with the nature and activities of the organsims and with the diagnosis, therapy, epidemiology and prevention of infectious diseases. Immunology has been closely associated with microbiology also in respect to serologic diagnosis, treatment with antiserums and active immunization.

Nature and Activities of Micro-Organisms

In the last half-century our concept of micro-organisms has greatly broadened with the realization that the ultimate control of infectious diseases depends to a large extent on a clear understanding of their activities. Improved methods of research have shown that bacteria, once considered the most primitive form of cellular organization, are complex organisms in many respects and are morphologically, chemically and physiologically similar to the higher organisms. Fluorescent and phase microscopy, ultraviolet-light photography and especially the electron microscope have delineated morphologic structures in bacteria and have even disclosed the shape, size and density of the viruses, many of which are beyond the resolving powers of the ordinary microscope. New staining technics have revealed previously unrecognized morphologic characteristics. For instance, the Feulgen technic for detecting desoxyribonucleic acid in nuclear material has disclosed the possibility of hereditary transmission of genetic characteristics in bacteria. Microchemical

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and spectroscopic analyses have determined the mineral and other constituents of the bacterial cell. Immunochemical technics have demonstrated differences in the proteins and carbohydrates of species and strains, such as the capsular polysaccharides of the pneumococci and the proteic M substance of the streptococci. By experimental technics it has been possible to produce variant strains of salmonellae characterized by different flagellar antigens.

The metabolic processes, enzyme systems, ability to synthesize vitamins and other essential substances and special nutritional requirements in the form of vitamins and growth-accessory factors have been at least partially determined for a number of species, although the complex mechanism of growth is as yet incompletely understood. Improved methods of cultivation have also facilitated diagnosis and have made possible the production of relatively pure bacterial products and toxins. Among these improvements are cystine as a medium for *Pasteurella tularensis*, media of low molecular composition for the production of diphtheria toxin, selective desoxycholate media for the isolation of the salmonellae, thioglycolate media for the cultivation of anaerobes and special media for accelerating the growth of the slowly growing tubercle bacillus.

The variability of micro-organisms not only is an interesting phenomenon but has an important bearing on virulence and antigenicity. Since 1906 the relation of the smooth, rough, mucoid and small colonial dissociation forms to the morphology, antigenic structure, virulence and metabolic activity of bacteria has been demonstrated by many investigators. Permanent spontaneous mutations occur in 1 out of 100,000 or 1,000,000 organisms. The great variability of viruses, which is shown by their adaptation to new hosts, to changes in pathogenicity (such as the 17D strain of yellow-fever virus or the fixation of the rabies virus in rabbits) and to the possible transmutation of smallpox to vaccinia virus, is of great epidemiologic and therapeutic importance. The development of drug-resistant strains of micro-organisms is a perplexing chemotherapeutic problem. The transformation of types in the pneumococci may be a genetic mutation brought about by a specific treatment. In certain bacteria morphologic variation even suggests a possible life cycle, as in the L-pleuropneumonia-like organisms of *Streptobacillus moniliformis*. New experimental methods are necessary to elucidate the mode of reproduction and life cycles of bacteria and to clarify some obscure associated aspects of the nature of infectious diseases. Nevertheless, it is interesting to speculate whether or not these plastic groups of micro-organisms have developed by a retrograde process from the autotropic bacteria to those dependent on the cells of the host for nourishment, to the rickettsiae and finally to the viruses.

The disease-producing power of an organism is determined by its transmissibility, invasiveness and ability to multiply and damage the tissues as modified by the resistance of the host. We have learned that the infectious agent must be able to penetrate the protective barriers that shelter the host from his environment, survive the many cellular and humoral defenses, find an environment suitable for multiplication and produce toxic substances or create conditions that cause pathologic disturbances in the host. For instance, an erythrogenic toxin-producing strain of hemolytic streptococcus may produce clinical scarlet fever in a completely susceptible person, in one with antitoxic immunity a streptococcic infection without a rash, and in one with both antitoxic and antistreptococcal immunity a transitory carrier state. Thus virulence, which is a complex summation of many complementary properties, can only be expressed in terms of a particular strain, a definite host and the exact conditions under which infection takes place.

Diagnostic Microbiology

The laboratory has become an important diagnostic aid in the fields of medicine and public health. Many and varied improvements have been made in the detection of pathogenic organisms by means of increased facilities for obtaining diagnostic material, by selective methods of culture and by the use of animals, the chick embryo and tissue cultures for the isolation of organisms cultivated with difficulty. Likewise, indirect methods of diagnosis, such as serologic and cutaneous tests, have undergone great development. The agglutination test in typhoid fever and other diseases, although recognized before 1900, has been perfected by the selection of strains, the use of flagellar, somatic and Vi antigens and the interpretation of results in naturally and artificially immunized persons. The precipitation test has been used in the classification of the hemolytic streptococci and other organisms and in forensic medicine. Complement-fixation and flocculation tests, of special importance in the diagnosis of syphilis, have been developed since 1900 and recently have proved of value in rickettsial, viral and protozoan diseases. Neutralization tests with protective antibodies have been especially useful in the diagnosis of viral diseases.

Microbiology and Epidemiology

Knowledge of the transmission of the various animal and human diseases has resulted in the conquest of water- and food-borne diseases and in the partial control of contact, air-borne and insect-borne diseases. Typhoid fever in countries with high sanitary standards has been reduced to a low incidence by the control of drinking water and milk, but despite full knowledge of the mechanism of its spread it has not yet been eliminated, because of endemic infections from undetected carriers. In

spite of similar knowledge, the control of endemic infections in institutions and outbreaks of food poisoning from the salmonellar and dysenteric organisms is still unsatisfactory. The control of diseases acquired through the respiratory tract either by direct contact or by aerial transmission is far from perfect, although in recent years considerable information has been acquired on the bacterial diseases caused by the streptococci, pneumococci, meningococci and diphtheria bacilli and on viral diseases such as influenza and psittacosis. Recognition of the transmission of *Pasteurella pestis* from rat to man by rat fleas has made possible the control of bubonic plague by the extermination of rats and rat fleas. The importance of carriers, particularly those with certain bacterial types, in the spread of diphtheria and meningitis has been realized. In the field of sanitation, considerable progress has been made in the transmission and control of enteric diseases. The pollution of water and edible mollusks has been detected by tests for coliform organisms and the effectiveness of chlorination has been established. Milk has been safeguarded by sanitary handling, pasteurization and the tuberculin testing of cattle. The importance of food sanitation and of the presence of carriers among food handlers has come to be appreciated. The aerial and direct respiratory spread of diseases, however, has only been partially controlled by the laying of dust by oil sprays and by the use of aerosol sprays and ultraviolet light to remove bacteria from the air in operating rooms, hospital wards, barracks and schoolrooms.

Microbiology and Treatment

Microbiology has played an important part in the production of antitoxins and in the development of specific chemotherapeutic agents, mostly synthetic organic chemicals or antibiotics. The activity of these agents is chiefly directed against bacteria and protozoa. Except for the psittacosis-lymphogranuloma venereum group, which is susceptible to sulfonamides and antibiotics, the viruses and rickettsiae are not affected. These agents act as specific inhibitors of essential metabolic functions by competition or neutralization, destroy vital morphologic structures or interfere with unidentified reactions concerned with synthesis or cell division. The discovery of new chemotherapeutic agents has been made by empirical methods, such as a chance observation of immediate importance, or by the systematic synthesizing and in vitro and in vivo testing of allied substances that may prove superior to a known drug.

Most antimicrobial agents are protoplasmic poisons for all types of cells, but some exhibit a selective action. For instance, penicillin, active against gram-positive cocci, is inactive against gram-negative bacilli and the cells of the host and gramicidin, active against gram-positive cocci, is only toxic to spermatozoa and erythrocytes, whereas tyrocidine is toxic to all tissues. A most interesting phase is the development of resistance to the chemotherapeutic agent by certain strains of microorganisms. The resistance of an organism to a given substance may evidently be modified by different types of variations, such as changes in metabolism and failure of the inhibiting substance to reach the susceptible cellular substrate. The mechanism of acquired resistance probably varies for different chemical compounds, but it appears to be largely effected through the overgrowth of latent mutants that are able to survive in the presence of the chemical agent, whereas the more numerous susceptible organisms perish.

Among the outstanding chemotherapeutic agents that have been developed by carefully planned research are the arsenicals for *Treponema pallidum* of syphilis and the trypanosomes of African sleeping sickness, the antimonials for the leishmania, the aromatic diamidines for the leishmania and trypanosomes, the aminoquinoline derivatives, especially chloroquine, for the plasmodia of malaria and the various sulfonamides and antibiotics for many species of bacteria. Although antibiotics had been known for years, their therapeutic application dates from the isolation of tyrothricin, the forerunner of gramicidin and tyrocidine, in 1939. Then followed the effective use of penicillin, a fungal product originally discovered in 1929, in the treatment of infections due to gram-positive bacteria, and in 1944 came the development of streptomycin from soil bacteria. The list of antibiotics that have revolutionized the treatment of infectious diseases includes gramicidin, penicillin, streptomycin, bacitracin, Chloromycetin, aureomycin and many others. Many have not fulfilled their early promise as general therapeutic agents, and the resistance of certain species of bacteria and the development of resistant strains have revealed their inadequacies. Nevertheless, our knowledge of chemotherapy is fast accumulating, new chemotherapeutic agents are being constantly acclaimed and the future holds promise that new and potent therapeutic agents will be developed through research in microbiology.

Teaching of Microbiology

The teaching of microbiology in our medical schools has undergone notable changes. In the first decade of the present century bacteriology was taught as an isolated science somewhat remotely related to medicine. After World War I the teaching of bacteriology began to acquire a diagnostic and clinical slant and to develop a closer correlation with clinical medicine, Nevertheless, some years elapsed before the concept that bacteriology and immunology should be taught as an integral part of diagnostic, therapeutic and preventive medicine was generally accepted. The final phase has been the transition of bacteriology into the broader

science of microbiology as a result of the opening of new fields in the viral and rickettsial diseases and of increased interest in medical mycology and protozoan diseases under the stimulus created by the problems of tropical medicine during World War II.

Immunity

Practically all our present knowledge of the mechanism of antibody-antigen reactions and its application to serology and supersensitiveness and of natural and acquired immunity to passive and active immunization has been derived in the last fifty years.

Antigen-Antibody Reactions

The mechanism of specific antigen-antibody reactions is gradually becoming clarified, and with advances in protein chemistry solutions to the many complex problems of immunochemistry will be found. Recent years have witnessed notable progress in the study of the many complex antigenic constituents of micro-organisms and in the immunochemistry of serum proteins. These highly molecular substances, mostly proteins, are capable of stimulating the formation of antibodies. The sharply specific antibodies, proteins of the serum-globulin class, are distinguished by minute differences in chemical or spatial configuration, are able to react with simple chemical compounds (haptens) as well as complex proteins and even may be directed at certain radicals of the antigen or at more than one determinative in the antigenic molecule. The use of conjugated antigens, in which definite substances are coupled with complex antigens, has shown that antibodies can react with a group of known chemical constitution in an antigen. This step alone has advanced the science of immunology to a stage at which the chemical composition of the group determining antigen-antibody specificity can be studied.

Serologic methods have proved effective micro-analytical tools in the hands of immunochemists in the study of micro-organisms and proteins; the action of specific autolytic enzymes, such as the polysaccharidases, in the differentiation of pneumococcic types, has proved even more specific than that of antibodies. Special antigens in micro-organisms may be identified by production of mutants deficient in one or more antigenic components, by selective inactivation with heat or chemicals or by absorption of serums with selected antigens. It has been found that flagellar antigens may exist in several forms (phase variation) and that the somatic antigens may contain polysaccharides that function only as haptens when extracted by drastic chemical methods but with milder methods are released as a phospholipid-protein-polysaccharide antigenic complex. The chemical nature and the biologic properties of these cellular components and the ease with which they come in contact with the tissues of the host are important in relation to the pathogenicity of a micro-organism and the immunity of the host.

The practical application of the newer knowledge of antigen-antibody reactions has proved of value in several fields. The serologic identification of specific proteins has been useful in microchemical analyses and in forensic medicine. Serologic tests, such as agglutination, precipitation, complement fixation and the detection of protective antibodies, have been of diagnostic value in infectious diseases. Toxins have been purified and concentrated and treatment with antitoxins has been made possible. Toxoids and vaccines have been used for the production of active immunity and of specific antitoxins and antiserums. Antibody-antigen reactions are also involved in supersensitiveness and blood groups, two fields of medicine not directly associated with infectious diseases.

Supersensitiveness

Supersensitiveness is a manifestation of an antigen-antibody reaction in which there is an abnormally exaggerated response to contact with an antigen. Present evidence indicates that anaphylaxis, bacterial allergy in infectious diseases and clinical allergies are essentially expressions of an antigen-antibody reaction. Improved methods developed with the isolated muscles of sensitized animals (Schultz-Dale technic) have facilitated the study of anaphylaxis in animals. Supersensitiveness to pathogenic micro-organisms, as typified by the tuberculin reaction in tuberculosis and the accelerated response to secondary vaccination with vaccinia, is now recognized as an expression of immunity to reinfection, although the reason that an allergic state develops in certain infectious diseases is unknown. The greatest progress has been made in the field of clinical allergy (atopy), which is a state of natural supersensitiveness in man often characterized by a hereditary tendency. It is due to a cellular reaction between an antigen (atopen) and a specific antibody developed by previous contact. Intracutaneous and patch tests, including the passive transfer of sensitization (Prausnitz-Küstner technic) have proved of diagnostic and therapeutic value in asthma and hay fever due to inhalent atopens, in food allergies due to ingestants, in cutaneous disorders due to chemical contactants and in drug idiosyncrasies.

Blood Groups

Notable advances have been made in blood groupings — so important in transfusions and in the identification of human blood and tissues in forensic medicine. The discovery by Landsteiner in 1901 that human blood contained A and B substances led to its classification into A, B, AB and O groups and explained the reactions in transfusions occasioned by the incompatibility of donor and re-

cipient. It was soon recognized, however, that cross-matching of the cells and serum of the donor with the serum and cells of the recipient was advisable because of the existence of subgroups. The hereditary transmission of the A, B and O genes and the application of mathematical predictions of inheritance to the legal question of paternity were established prior to 1925. A second method of grouping blood cells by M and N substances, which were confined exclusively to the erythrocytes and were detectable only by antiserums from immunized animals, was discovered in 1927. The M and N classification has doubled the chances of a man's escaping wrongful accusations in paternity suits. The application of blood groupings to the science of anthropology and to the movements and distribution of the races of man has been demonstrated by the detection of blood groups in human remains, such as mummies, and in the percentile variation of the several blood groups throughout the world. The last important advance was the discovery in 1940 of the Rh factor in simian and human blood and its subsequent association with undesirable reactions in transfusions and with the production of erythroblastosis fetalis in infants by incompatibility between an Rh− mother and an Rh+ fetus. Further studies have revealed that there are several Rh antigens of different capacities that complicate Rh typing and the production of antibodies.

Immunization

Passive immunization, although at present overshadowed by modern chemotherapeutic agents, has proved of therapeutic value when appreciable quantities of protective antibodies are needed immediately. Improvements in the production of diphtheria antitoxin include the production of a relatively pure toxin by growing the organisms in media containing no substances of greater molecular weights than the amino acids and by removing extraneous material, the purification of the antitoxic serum by eliminating the horse-serum proteins and by separation of the pseudoglobulins that contain the antitoxin, and new methods for the rapid testing of potency. Similarly, tetanus toxin and antitoxin have been purified, concentrated and standardized. In recent years antitoxins have been prepared against the several types of *Clostridium botulinum*, *C. welchii*, other gaseous gangrene organisms and hemolytic streptococci for the differentiation of types and sometimes for therapy. Therapeutic serums that contain antibodies against the cellular products of micro-organisms have been produced for certain types of meningococcus, influenza bacillus and pneumococcus.

Active immunization may be effected by natural exposure to an infectious disease or by the artificial injection of living or dead organisms, their toxins or their antigenic components. Protection may be afforded by the injection of small doses of toxin (scarlet fever), by the use of toxin-antitoxin mixtures (diphtheria) or by the inoculation of toxoids (diphtheria, tetanus). In recent years standardized toxins and toxoids of high potency and purity have been prepared. Active immunization with diphtheria and tetanus toxoids has been an outstanding achievement. The proper doses, methods of administration, optimal intervals and number of injections have been established. The value of combined adjuvant immunization has been discovered. Practical tests for evaluating the efficiency of inoculations have been developed, such as the Schick test in diphtheria and the various methods of measuring the protective, antitoxic and antibody titer of the serums of immunized persons. Likewise, the need of booster doses when contact with natural infection has become negligible has become apparent.

The production of immunity by vaccination with living or dead organisms has been used in a number of diseases. Immunization against viral diseases requires living organisms or large doses of killed organisms. Living organisms have been used against psittacosis, yellow fever, smallpox and rabies with more or less success. Immunization with living viruses has been effected by administration through unnatural routes (psittacosis), by strains that have developed a low virulence for man (yellow fever, rabies) and by immunologically related strains (vaccinia for smallpox). Some success has been obtained with formalized vaccines (equine encephalomyelitis, rabies and influenza). The use of BCG (Bacillus Calmette–Guérin) for the prophylaxis of tuberculosis is an instance of immunization with a slightly toxic attenuated strain of the tubercle bacillus. Statistical proof of its efficiency is fast accumulating, and the millions of inoculations indicate that there is no practical danger of the reversion of the organism to a virulent state. The use of killed strains of high antigenicity and the inclusion of the flagellar, somatic and even Vi antigens have improved the protective powers of the typhoid vaccine. The prophylactic value of vaccines prepared from killed, fresh, smooth, virulent Phase I *Hemophilus pertussis* has been established in whooping cough. Vaccines of killed organisms have also proved more or less effective in brucellosis, pneumonia, cholera, plague, typhus, Rocky Mountain spotted fever and other diseases.

Bacteria

Modern methods of diagnosis, treatment, epidemiology and prevention of the bacterial diseases have been either wholly derived or greatly perfected in the last fifty years. Little notable progress, other than in treatment and epidemiology, has been made since 1900 in the study of certain pathogenic bacteria, such as the bacilli of anthrax, glanders and leprosy. On the other hand, certain important pathogenic bacteria, such as the etiologic

agents of pertussis, tularemia, ratbite fever, bartonellosis and the various spirochetal diseases, have been discovered, their morphologic, biochemical, physiologic and cultural characteristics and pathogenicity described and their relation to their respective diseases elucidated. Likewise, most of the important facts concerning the activities of many organisms discovered before 1900 have since been disclosed. A few representative bacteria have been selected to illustrate the progress of medical bacteriology.

The diverse activities of the streptococci, among the earliest isolated bacteria, have only recently been recognized. The hemolytic streptococci have been separated in groups on the basis of group-specific polysaccharides. Studies have been made of their toxic products — especially the erythrogenic scarlet-fever toxin. Their etiologic relation to scarlet fever, septic sore throat, erysipelas, bronchopneumonia and bronchitis, puerperal sepsis and probably rheumatic fever has been established. Aerial as well as direct respiratory transmission from dust-borne organisms has been demonstrated and the incidence of respiratory infection has been reduced by bactericidal sprays and dust-laying oils. The genus Salmonella includes the typhoid and paratyphoid bacilli and about 150 other species or varieties that are associated with food poisonings or generalized infections. The outstanding advances in this genus have been the serologic classification and identification of the organisms by their somatic and specific and nonspecific flagellar antigens, the development of selective media for their isolation and the recognition that certain species are prevalent in different parts of the world. At least four salmonellar species appear to be of human origin; the remainder seem to be of mammalian and avian derivation, although they produce in man a transitory enteritis (food poisoning) or systemic infections, or both. Since the isolation of *Hemophilus pertussis* in 1906, its etiologic role in whooping cough has been demonstrated beyond reasonable doubt, diagnostic methods have been perfected and the value of prophylactic vaccination has been proved.

Plague represents an insect-borne disease, primarily of animal origin, that has been associated with rats, ships and movements of populations for centuries. Although the organism, *Pasteurella pestis*, was isolated in 1894, the interrelation of the bubonic, septicemic and pneumonic types of the disease, the role of the rat flea in the transmission of the disease from rat to man, the relation of sylvatic plague in wild rodents to the disease in rats and man, the aerial and contact transmission of the pneumonic type and active immunization with vaccines have been discovered in the present century. In 1918 the previously unrelated *Brucella melitensis*, the cause of Malta fever in goats and man, and *Br. abortus*, the cause of infectious abortion in cattle and of undulant fever in man, together with *Br. suis* were found to belong to the same genus. Since that time the differential characteristics of these organisms, their pathogenicity for man and animals, their transmission by contact and through milk, the existence of undulant fever in man and the prophylactic vaccination of cattle have been established. The various lines of progress in the study of the tubercle bacilli include cultural and pathologic differentiation of the human, bovine, avian and cold-blooded animal species, observations on colonial dissociation, new fluid media for rapid growth, improvements in the intracutaneous and patch tests with purified tuberculin, active immunization with BCG and immunologic and epidemiologic studies. The reduction of bovine tuberculosis in children in the United States by the pasteurization of milk and the control of tuberculosis in cattle has been an outstanding achievement.

Although the common spirochetal diseases, particularly syphilis, have been known for many years, the morphologic, biochemical, physiologic, antigenic and cultural characteristics of the causative organisms, their classification and pathogenicity, the immune reactions of the host and the treatment and epidemiology of the diseases have been entirely products of the present century. The treponemal agents of syphilis and yaws were discovered in 1905; those of pinta, in 1940. Extensive investigations on syphilis have revealed the pathogenicity of *Treponema pallidum* in rabbits and man, the value of the Wassermann and flocculation tests for diagnosis and control of treatment, the immune reactions of man and the success of treatment with arsenicals and antibiotics. *Borrelia recurrentis*, the causative agent of epidemic louse-borne relapsing fever, and *Borrelia duttoni* and other species that cause endemic tick-borne relapsing fever in different parts of the world have been isolated and classified, and the epidemiology, transmission and immunity of their respective diseases have been established. Since the isolation of *Leptospira icterohaemorrhagiae* as the cause of Weil's disease in 1914, the more frequent, less fatal, nonicteric form of the disease has been recognized and its transmission by contact with water or material contaminated by the urine of carrier rats has been confirmed. Some fifteen pathogenic species of *Leptospira* in different parts of the world, such as *L. canicola* of the yellow jaundice of dogs, *L. grippotyphosa* of European swamp fever and *L. hebdomidis* of Japanese seven-day fever, have been classified serologically.

Fungi

In recent years the fungi have gained increasing prominence as agents of infectious diseases, although most of the important species were recognized before the turn of the century. Coccidioidomycosis, caused by *Coccidioides immitis*, is no longer considered a

rare, highly fatal granulomatous systemic infection of the lungs and other viscera but is now recognized as an early acute pulmonary infection that is self-limited, like tuberculosis, in most instances and only occasionally produces extensive pulmonary and extrapulmonary lesions. Intracutaneous tests with coccidioidin and cultural studies indicate a high rate of infection in the arid areas of the southwestern United States by the aerial transmission of dust-borne spores from the soil, which is probably contaminated by rodents. Our knowledge of the pathology, the characteristics of the etiologic organism and the diagnosis of American and European blastomycosis has expanded. The fungal origin of histoplasmosis, a rare disease resembling infantile kala-azar, was first recognized when the organism, *Histoplasma capsulatum*, was cultured in 1934. The fungi imperfecti, especially the dermatophytes, have been classified by their morphologic and cultural characteristics and pathologic activities, and the various species of *Microsporum*, *Trichophyton*, *Epidermophyton* and *Endodermophyton* have been associated with specific skin diseases. The immunity, therapy and diagnosis of fungous diseases present attractive prospects for future research, and the mycologic laboratory is fast becoming a necessary adjunct for the modern dermatologic clinic.

Rickettsiae

The pathogenic rickettsiae, entirely unknown in the past century, represent one of the most interesting fields in microbiology. The rickettsiae apparently occupy an intermediate position between certain cytotrophic bacteria and the viruses. They are small, nonmotile, gram-negative, diplobacillus-like, intracellular, often pleomorphic organisms, 0.3 to 2.0 microns in length. The rickettsial diseases, although widespread throughout the world and of variable manifestations, have certain similar characteristics. They are transmitted by insects, probably have a rodent reservoir host, reveal transitional varieties and exist in endemic and epidemic forms. These diseases comprise the typhus, spotted fever, tsutsugamushi and Q-fever groups and certain miscellaneous entities.

All our information concerning the characteristics, identification and pathogenicity of these organisms and of the immunity, treatment, epidemiology and prevention of the rickettsial diseases has been derived in the last fifty years. The two organisms of the typhus group, *Rickettsia prowazeki* of epidemic or louse-borne typhus, and *R. typhi* of endemic or flea-borne murine typhus, have been differentiated pathogenically and serologically, their pathogenicity in animals and man has been studied and preventive measures such as the destruction of the insect vectors and rodent hosts and prophylactic vaccination have been evolved. *Dermacentroxenus rickettsi* of Rocky Mountain and Brazilian spotted fever and *D. conori* of boutonneuse fever and Kenya fever have been distinguished from the other rickettsiae; their pathogenicity and their cyclic transmission through ticks have been established, diagnostic methods have been perfected and prophylaxis of Rocky Mountain spotted fever by vaccines has been developed. The several varieties of *Rickettsia tsutsugamushi* in Japan, the East Indies and the southwest Pacific produce clinically similar diseases, known as tsutsugamushi, or popularly as scrub typhus or mite fever. The etiologic organisms are transmitted by larval trombiculid mites that live on voles in Japan and on field rats in the East Indies. Information on this group of diseases is still far from complete; further investigations are needed to test the effectiveness of vaccination and to develop preventive measures other than the destruction of the mites and the chemical mite-proofing of clothing. It has been shown that the organisms of Q fever, *R. burneti* of Australia and *R. diaporica* of the United States, are serologically identical and that they differ only in species of tick vector and other minor epidemiologic aspects. New rickettsial organisms, such as *R. akari* of rickettsialpox, are being reported, and possibly others will be discovered in the future.

Viruses

The viral diseases have been known clinically for many years, but their etiologic agents have been recognized only during the past few decades. The viruses that produce serious diseases in animals and plants range from a size just visible in the microscope to one of 10 microns, which is far beyond the limits of visualization, but they are not sharply delineated from the bacteria or rickettsiae in size or filterability. Considerable information has been obtained concerning the structure, size, form and chemical constituents of the viruses by means of the electron microscope, ultracentrifugation, collodion filtration and microchemical assays. When purified by precipitation and ultracentrifugation their structure has been found to be qualitatively similar to that of highly organized living matter. The virus of the tobacco mosaic disease has even been obtained as a crystalloid substance, but the classical chemical evidence of molecular structure is lacking. In certain diseases viruses manifest their presence by the formation of intracellular inclusion and elementary bodies, the latter apparently constituting the viral particles. Viruses have been cultivated in the chick embryo and in tissue cultures.

Viruses are chiefly recognized by their capacity to produce infection in susceptible cells or hosts. The number of viral particles necessary to produce infection ranges from 2 in the T_2 bacteriophage for *Escherichia coli* to as high as 50,000,000 in rabbit papilloma. Their virulence and pathogenicity may be titrated in terms of the lethal dose in small animals and chick embryos. Some viruses are highly

specific and others are of low specificity; instances have been encountered of the adaptation of mutant strains to a wider range of hosts. The resistance of the host varies with species, age and nutrition. Natural acquired immunity is often of long duration, such as that to yellow fever, mumps, vaccinia and measles, but its persistence is extremely short in influenza and the common cold. Viral infections may be diagnosed by cultivation of the virus in the chick embryo, by animal inoculation, by neutralization tests with serums of the patients, by complement fixation and agglutination in yellow fever, vaccinia, psittacosis, influenza and lymphogranuloma venereum and by the agglutination of the erythrocytes of the fowl by certain viruses such as influenza, mumps and the Newcastle disease of chickens, either directly or indirectly in connection with neutralization tests.

The bacteriophages, discovered in 1915, are of particular interest. They are probably viruses that attack bacteria, although their biologic nature is still uncertain. They have all the morphologic chemical and physical attributes of the pathogenic viruses. They multiply by lysis of bacteria, possess antigenic properties and immunologic relations and exhibit variation. The existence of resistant and susceptible strains of bacteria to specific bacteriophages has permitted their classification and epidemiologic identification by bacteriophage typing.

Some achievements in certain viral diseases may be mentioned. Devastating animal diseases, such as foot and mouth disease, have been controlled by rigid quarantine and the slaughter of infected animals. Such methods are not applicable to human diseases aside from the control among animals of diseases such as psittacosis and rabies, which affect both man and animals. Smallpox was long ago subdued by vaccination. Modern advances in this field have been improvements in the preparation, potency and sterility of the vaccinial virus, the technic of inoculation and the interpretation of the reaction of immunity. The mosquito transmission of yellow fever was proved in 1900 and epidemic yellow fever has been practically eliminated by the control of its vector, *Aedes aegypti*, but the endemic jungle type of yellow fever can only be combated by vaccination with the stabilized, nonlethal 17D strain of the virus. The existence of yellow fever in certain regions has been determined in surveys by means of liver biopsies and neutralization tests with blood serums. Influenza may possibly be held in partial subjection by repeated vaccination with purified formalized vaccines prepared from A and B types, but the efficiency of these vaccines is still uncertain.

Poliomyelitis still presents an outstanding challenge. No means has been devised for preventing or curing the acute infection. Its transmission is not fully understood, although the presence of the virus in the tonsillar nasopharyngeal region and in the intestine suggests transmission by direct and indirect contact with healthy carriers and by food, water and flies. The existence of closely similar viruses complicates the epidemiologic picture. Laboratory diagnosis is handicapped by lack of susceptible animals other than monkeys for protection tests, although the questionable Lansing strain has been adapted to mice. Active immunization with the living virus has proved dangerous and impractical. Vaccines prepared from the spinal cords of rabbits infected with the fixed virus, attenuated by drying or inactivated by phenol or ultraviolet light, are used for the prophylaxis of rabies in infected persons, although the virus has been cultivated in the chick embryo. The prevention of rabies, however, depends on the control and immunization of dogs. Epidemiologic studies of the encephalitides (St. Louis encephalitis, equine encephalomyelitis, Japanese B encephalitis and so forth) have shown that their prevention is dependent on the control of the mosquito vector and possibly on the prophylactic vaccination of persons exposed to infection.

Psittacosis, a highly fatal viral disease of man that is acquired from carrier birds, has been controlled by quarantining psittacene birds. The diagnosis of lymphogranuloma venereum by the Frei skin test and complement fixation and its successful treatment, as well as that of psittacosis with sulfonamides, have been accomplished. The viruses of measles and mumps have been cultivated, their antigenicity and antibodies studied, their transmission to man observed and the prophylactic use of normal serum, placental extracts and especially gamma globulin in measles demonstrated.

Protozoa

Our understanding of the characteristics, pathogenicity and immune reactions of the pathogenic protozoa of man and the treatment, epidemiology and prevention of protozoan diseases has been largely acquired since 1900, although the important parasites and their clinical diseases were previously known.

The pathology of amebiases was not completely described until 1901, although the causative agent, *Endamoeba histolytica*, was associated with amebic dysentery as early as 1887. With recent cultural methods it has been possible to study the morphology, cyst formation, nutritive requirements, rate of growth, virulence and pathogenicity of different strains and to produce abundant uncontaminated material for antigens in serologic tests and for the in vitro testing of chemotherapeutic agents. Diagnostic methods have been improved by criteria for differentiating nonpathogenic intestinal amebae, such as new technics of proctoscopic examination, cultures and complement fixation. Effective chemotherapeutic agents such as emetine, carbarsone, chiniofon and Diodoquin have been developed since 1912. The method of transmission through food,

flies, water and personal contact and the importance of carriers (particularly food handlers) have been determined.

Since 1901 considerable information has accumulated concerning the metabolism, nutritive requirements and cyclic development in mammalian and insect hosts of the pathogenic trypanosomes of man and concerning their evolutionary relation to the trypanosomes of animals. The South American *Trypanosoma cruzi* grows readily on artificial media, but the African *T. gambiense* and *T. rhodesiense* have been cultivated only recently and without notable success. The pathologic lesions and the immune reactions of the mammalian hosts have been described. Methods of diagnosis, including the microscopic identification of the trypanosomes in the blood, spinal fluid or tissues, animal inoculation, complement fixation and xenodiagnosis, have been perfected. Effective chemotherapeutic agents for the treatment and prophylaxis of African trypanosomiasis, such as antropol, tryparsamide, the aromatic diamidines and Mel B have been evaluated in animals and man. Preventive measures, such as the destruction of riverine and bush tsetse flies and reduviid bugs, the reduction of animal hosts and the protection of man from the insect vectors, have been evolved.

Similarly the three leishmanian parasites, *Leishmania donovani* of kala-azar, *L. tropica* of oriental sore and *L. braziliensis* of American mucocutaneous leishmaniasis, have been recognized since 1903 and their nutritive requirements, their cultural characteristics and the relation of the flagellate cultural forms to the leptomonad forms in insects and the leishmanian forms in the mammals have been elucidated. The incrimination of Phlebotomus flies as the insect vectors, for years a controversial subject, has been confirmed experimentally. Also, the mechanical transmission of the parasites by stable flies or mosquitoes and by direct contact has been demonstrated. The dry and the moist forms of oriental sore, which differ epidemiologically, have been distinguished. The diagnosis of kala-azar has been effected by the microscopic identification of the organisms in the blood, spleen, liver and bone marrow, by complement fixation with antigens of acid-fast bacilli and by flocculation tests. The diagnoses of the cutaneous leishmaniases have been made by the identification of the organisms in the tissues and by intracutaneous tests. Active immunization against *Leishmania tropica* and *L. braziliensis* has been produced with living organisms. In vivo tests on animals and on man have revealed the value of the pentavalent antimonials and aromatic diamidines in kala-azar, the trivalent antimonials in American mucocutaneous leishmaniasis and local infiltrations of emetine and berberine in oriental sore.

The three important malarial parasites of man were recognized and the asexual erythrocytic cycle in man and the sexual cycle in anopheline mosquitoes were described before 1900. Since that time there have been great advances in our knowledge of malaria and of the plasmodia of man. The pre- and exoerythrocytic cycles have been followed in avian plasmodia and to a lesser extent in simian and human plasmodia, and the relation of exoerythrocytic forms to the production of relapses has been postulated. The metabolism, oxygen requirements, glucose utilization and viability of avian and simian plasmodia in tissue and blood cultures and in the chick embryo have been determined. The pathogenicity of different strains and species has been tested in volunteers in respect to virulence, incubational period, clinical severity and relapses. The pathologic effect of the plasmodia on the red blood cells, bone marrow, reticuloendothelial system and various tissues and the early and late infection in volunteers have been studied. Diagnostic methods have been improved by the use of the thick-film and concentration methods for the blood, by bone-marrow biopsies and by complement-fixation tests with antigens from simian or avian plasmodia. The resistance of man to different strains has been studied and hyperimmunization with living trophozoites or sporozoites has been carried out, but further investigations are required. Chemotherapeutic agents such as Atabrine, plasmoquine, chloroquine and Paludrine have been developed as the result of the extensive in vitro and in vivo screening of large numbers of synthetic organic chemical compounds against avian and simian plasmodia and of the final testing of selected compounds against standard strains of *Plasmodium vivax* and *P. falciparum* in man. However, the perfect drug that will destroy the invading sporozoites, the asexual erythrocytic and exoerythrocytic forms and the gametocytes and that will act as a causal prophylactic has not yet been found. The present drugs eliminate the clinical symptoms in patients and have a suppressive action in persons exposed to infection but have only a moderate curative or causal prophylactic action. Malaria has been lessened in many parts of the world by the reduction of anopheline mosquitoes through drainage or treatment with larvicides of their breeding grounds and the spraying of houses with insecticides, by the detection and treatment of gametocyte carriers and by protecting susceptible subjects with mosquito screening or through suppressive drugs.

Future Progress

It is interesting to speculate on the progress in microbiology in the next fifty years. At first glance it seems improbable that the rapid progress of the past half-century can be maintained, during which period immunology became a fully-developed science; antibiotics, other chemotherapeutic agents and biological products revolutionized treatment and

prophylaxis; the agents of viral and rickettsial diseases were discovered; and the causative organisms of many bacterial, fungal and protozoan diseases were disclosed. It appears more likely that progress in the immediate future will be chiefly confined to extending, consolidating and applying the knowledge previously acquired from the important discoveries of the past. Yet, despite this general impression, it is not impossible that the next fifty years may produce events as spectacular even as those of the past half-century.

215 Main Street

CASE RECORDS OF THE MASSACHUSETTS GENERAL HOSPITAL

Weekly Clinicopathological Exercises

FOUNDED BY RICHARD C. CABOT

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CASE 37141

PRESENTATION OF CASE

A fifty-nine-year-old woman was admitted to the hospital complaining of abdominal distention and dyspnea.

Seven years prior to entry, breathlessness on exertion had been treated by her physician with daily doses of 0.1 gm. of digitalis. This was continued for the following six years with a subjective feeling of well-being. Nine months before entry for a period of three weeks she had marked nocturnal dyspnea accompanied by severe exertional dyspnea, which caused her to be hospitalized elsewhere. After discharge, although somewhat short of breath, the patient continued to care for herself until she was readmitted to the hospital because of ankle edema and marked abdominal swelling. Treatment consisted of daily potassium and ammonium chloride, frequent mercurial injections and sodium restriction. She improved after three weeks and was discharged; but again edema of the lower extremities worsened, the abdominal girth increased and paroxysmal nocturnal dyspnea occurred on several occasions. For several weeks she also complained of a slight nonproductive cough not associated with hemoptysis or chest pain. Immediately prior to entry the patient believed that she had been slightly oliguric. Three years ago, after a positive Wassermann test, she was treated with arsphenamine and bismuth, and a full course of penicillin was given during the recent hospitalization.

There was no past history of tuberculosis, hypertension, scarlet fever, chorea or rheumatic fever.

On physical examination the left eye showed corneal scarring and divergent strabismus. Some pitting edema of the right breast was noted, although no mass could be palpated. The neck veins were distended with the patient in the sitting position. Bilateral basal dullness was percussed posteriorly to the midscapula on the right; on auscultation diminished breath sounds were heard over both lung fields and moist fine rales were present at the bases. The heart was enlarged to the left, with the point of maximum impulse diffusely visible in the fifth intercostal space about 10.5 cm. from the midsternal line. There was an apical middiastolic rumble and a +++ systolic non-transmitted murmur. No thrill was felt. The pulmonic second sound equaled the aortic. The liver edge was sharp, regular and smooth, although no other organs were palpable because of the presence of ascites, which distended the abdomen. A cystocele was noted in an otherwise normal pelvis, and the rectal examination was normal. Four-plus pitting edema of the extremities was noted, with some edema over the sacrum. The fingers were not clubbed.

The temperature was 99°F. and the pulse 120. The blood pressure was 120 systolic, 80 diastolic.

Urinalysis revealed an acid dark-yellow urine with a specific gravity of 1.011, a + test for albumin, no sugar and no bile; the sediment contained many bacteria, rare red cells and a solitary granular cast per high-power field. Examination of the blood showed white-cell counts of 6500 and 14,000, with normal differentials. The hemoglobin varied between 12.5 and 13.5 gm. Three stools were guaiac negative. The alkaline phosphatase was 7.4 units, the total van den Bergh 8.8 mg., the total protein 6.98 gm., the albumin 4.38 gm., the globulin 2.60 gm. with a ratio of 1.7 and the nonprotein nitrogen 80 mg. per 100 cc.; the sodium was 133.9 milliequiv., the chloride 93 milliequiv., the carbon dioxide 22.6 milliequiv., and the potassium 5.3 milliequiv. per liter. A bromsulfalein test disclosed an 18 per cent dye retention in forty-five minutes. The prothrombin time was 54 per cent and the cephalin flocculation ++ in forty-eight hours. An x-ray film of the chest showed an enlarged heart; the oblique view suggested right-ventricular enlargement with a prominent pulmonary artery. A good-sized pleural effusion was seen on the right and a number of calcified scars were present in the left lung field.

Since there was a persistent rapid apical rate, 0.5 mg. of digoxin was given daily to ascertain whether the patient was fully digitalized. Nausea, dizziness and bigeminy indicated toxicity after a

few days and the patient was maintained on a salt-free diet and 7.5 gm. per day of ammonium chloride, awaiting improvement from toxicity. Abdominal paracentesis was done, with removal of 2300 cc. of amber-colored serous fluid having a specific gravity of 1.018 and containing 8 to 15 red blood cells per high-power field and an occasional epithelial cell. Thoracentesis was done on the right, with withdrawal of 1000 cc. of amber-colored, serous fluid resulting in much easier breathing. An electrocardiogram taken following removal of fluid indicated auricular fibrillation, digitalis effect and right-axis deviation. The QRS interval was 0.08 sec. The R wave was tall in Leads V and AVR; the S wave was broad in Lead V_6; the ST segment was sagging; the T waves were low in Leads 2, V_3, V_4, V_5 and V_6. The patient complained of hoarseness; a laryngologist noted good movement of both cords, with slightly diminished excursions of the left vocal cord.

Bleeding from the paracentesis wound required suturing, although oozing continued from needle-puncture sites. In the morning of the following day, the systolic blood pressure was recorded as 80; twenty minutes later it was unobtainable and the patient had become unresponsive. The reflexes were normal. She showed mild cyanosis of the lips and nails. The abdomen was slightly distended, without spasm, and peristalsis was present. The temperature, hemoglobin, white-cell count and urine specimen obtained by catheterization were all normal. A chest film was not remarkable, although the stomach was seen to be distended. An electrocardiogram showed no evidence of potassium toxicity (the serum potassium was 5 milliequiv. per liter). The carbon dioxide, however, was 6 and 8 milliequiv., the chloride 125 milliequiv., and the sodium 133 milliequiv. per liter; the nonprotein nitrogen was 87 mg. per 100 cc. A left-lower-quadrant abdominal tap was done, revealing a small amount of blood fluid that showed only crenated red-blood cells microscopically. A Levine tube was passed to deflate the stomach and 560 cc. of one-sixth molar solution of lactate was given intravenously without evidence of change. The patient remained unconscious without obtainable blood pressure or urine output for twenty-four hours and then died quietly.

Differential Diagnosis

Dr. Robert S. Palmer*: On the basis of the history and the physical examination, I judge that this patient had congestive heart failure. Was the congestive heart failure of seven years' duration or was it of only nine months' duration? Seven years before entry she was digitalized for exertional dyspnea and seemed to get along all right, but was the improvement due to natural causes or to the treatment given? At any rate, she undoubtedly had congestive heart failure for nine months. During that time she had an increase in girth. Since she had ascites when she was admitted, I suspect she had gradually developing ascites. She may have had constrictive pericarditis and tricuspid-valve disease, since these two conditions are commonly associated with a large liver and with ascites. With constrictive pericarditis there is usually a small heart, although occasionally the heart may be large. The age of the patient is somewhat against constrictive pericarditis, since it is more likely to occur in younger people.

May I see the x-ray films? Did this patient have a prominent or a huge pulmonary artery, or a large right heart?

Dr. Stanley M. Wyman: The x-ray films were all taken with the patient supine; therefore it is very difficult to be certain that the apparent size of the heart is not partially due to magnification. I cannot outline the right border of the heart, so part of the apparent increase in size toward the left may be due to displacement of the heart. There is rather significant right pleural effusion, obliterating the costophrenic angle and the right leaf of the diaphragm. The pulmonary artery is prominent, but I do not believe it is huge. There are enlarged hilar and pulmonary vessels, and the vessel-shadows extend well out into the lung fields and are quite large. All these findings are consistent with pronounced pulmonary congestion.

Dr. Palmer: Is there any actual bulge in the heart shadow that makes you think the left auricle is enlarged?

Dr. Wyman: I cannot make a statement about the auricle; it does not seem huge, but the films are not of such quality as to exclude that possibility.

Dr. Palmer: Is the aorta normal?

Dr. Wyman: It is normal in size.

Dr. Palmer: From the history, the physical examination and the laboratory findings, the patient had failure of the heart, liver and kidneys. However, the primary disease was in the heart. The history suggests that she had syphilis and there were corneal scars and strabismus, which may have been on a syphilitic basis, but there was nothing in the physical examination to make me think she had syphilitic heart disease. She may have had congenital heart disease, but there was nothing to suggest this except the marked right heart failure. No murmur was found early in the course of the disease. A rare possibility is the so-called Lutembacher's syndrome — that is, the combination of an auricular septal defect with mitral stenosis, either congenital or acquired. This syndrome is believed by many to be rheumatic. Patients with this difficulty live to good ages and sometimes get along very well without ever presenting the cyanotic form of congenital heart disease. The picture given in the original description was that of a small aorta and a huge pulmonary artery. These findings are not present in this case.

*Physician, Massachusetts General Hospital.

I think this patient had mitral stenosis, because of the murmur, and therefore had rheumatic heart disease. Because of heart failure and the large liver and ascites I think she also had tricuspid regurgitation. The right-axis deviation noted in the electrocardiogram is consistent. I shall list as my basic diagnoses rheumatic heart disease, mitral stenosis and a question of tricuspid valvular disease. I do not think she had constrictive pericarditis or Lutembacher's syndrome. She had been in failure and was on bed rest, so there may have been one or more pulmonary emboli that in the latter part of the illness produced cor pulmonale.

The patient had an enlarged liver, and the prothrombin time and the cephalin flocculation indicated liver involvement. I do not think she had a syphilitic liver, as that does not produce a large smooth liver but a large lobulated one. I cannot exclude cirrhosis; I am told nothing about her habits. I think she had an engorged liver secondary to the heart disease. She may have cardiac cirrhosis, since the congestive failure has been present long enough.

The patient had a + albumin in the urine, and bacteria, rare red cells and a granular cast in the sediment. She also had a nonprotein nitrogen of 80 mg., which means that she had kidney impairment and failure. She may have had nephrosclerosis or pyelonephritis. There was no evidence of glomerulonephritis. I think she had a congestive kidney secondary to the primary heart disease.

The most important thing for me to decide is the cause of death. Also, did the death come about naturally or was it hastened by any treatment she may have received? The patient was acidotic and had been given a large dose of ammonium chloride. With electrolytes, as with other things, not absolute values but proportions are important. She had what amounted to a primary sodium deficiency — the chlorides were very high, the sodium was not affected and there was acidosis. Presumably there was very little plasma bicarbonate. I think that best explains the situation and may possibly have contributed to the state of shock. In that case the pathologist may not be able to tell us the cause of death. I have often wondered if we should ask for bionecropsies to determine the electrolyte balance in the tissues at the time of death.

The patient had bled from the paracentesis wound, so hemorrhage may have occurred. She also had a distended abdomen. The fact that peristalsis was present is against peritonitis. It is extremely difficult to recognize either hemorrhage or infection in a patient in shock. I do not believe hemorrhage was the cause of shock.

I think the cause of death was congestive failure, with shock and with profound acidosis.

DR. ALEXANDER LEAF: May I make a comment on the use of acidifying diuretics in a case like this? When this patient entered the hospital she had an elevated nonprotein nitrogen and a reduced carbon-dioxide content of the serum, indicating some degree of renal insufficiency with acidosis, so that she was already having difficulty getting rid of acid metabolites. In spite of this pre-existing acidosis she was edematous and not excreting sodium. As the acidifying diuretics act only by virtue of the tendency toward acidosis they produce, it can be anticipated that their use in an edematous subject who is nevertheless acidotic will be of little value. Such was the case here. Increasing the severity of the acidosis by administering ammonium chloride is likely only to be harmful to the patient and to have little if any beneficial effect on the edema.

Secondly, I should like to support Dr. Palmer's contention that the patient's severe acidosis may have been an important contributory cause of death. When the carbon-dioxide content of the serum falls as low as 8 milliequiv. per liter, as it did in this patient, the only way by which the body can keep the pH of its fluids within the limits compatible with life is to blow off carbon dioxide by hyperventilation, thus reducing the carbonic-acid concentration in the body fluids, which will result in some compensation of the acidosis. But when a considerable portion of lung suddenly loses its functional capacity as the result of a large pulmonary embolus, as occurred in this patient, the ability to compensate for the acidosis may be abolished and the pH of the body fluids may drop below the limit compatible with life. So although one does not find pathologic evidence of acidosis at post-mortem examination, uncompensated acidosis may nevertheless have been the terminal event.

CLINICAL DIAGNOSES

Rheumatic heart disease with mitral stenosis, mitral insufficiency and auricular fibrillation.
Uremia.
Cirrhosis of the liver.

DR. PALMER'S DIAGNOSES

Rheumatic heart disease with mitral stenosis and tricuspid-valve disease.
Congestive heart failure.
Congestive kidney.
Congestive liver, ?cardiac cirrhosis.
Profound acidosis.

ANATOMICAL DIAGNOSES

Rheumatic heart disease with marked mitral stenosis and slight aortic stenosis.
Patent foramen ovale.
?Lutembacher's syndrome.
Embolus, right pulmonary artery.
Severe passive congestion.

PATHOLOGICAL DISCUSSION

DR. TRACY B. MALLORY: The heart was found to be hypertrophied, and there was a well marked

mitral stenosis, as Dr. Palmer predicted. The interauricular septum was anatomically patent and easily admitted the passage of the tip of the index finger, but since the flaps overlapped with a considerable margin it may have been functionally closed. This may be an example of the Lutembacher syndrome, as there is a considerable range both in the degree of mitral stenosis and of patency of the interauricular system.[1] The mitral valve showed a very characteristic chronic rheumatic lesion. There were also traces of involvement of the aortic valve — not enough to have produced any functional deformity but enough to reinforce the anatomic diagnosis of old rheumatic involvement of the endocardium. The best anatomic explanation for death that we could find was a very large embolus filling the right pulmonary artery, which appeared to be of some age, since it was adherent. This may have been a paradoxical embolus, since there was a mural thrombus in the left auricle and a patent foramen ovale. I like Dr. Leaf's explanation of the mechanism by which it could have contributed to the acidosis by impairing the compensatory function of a large segment of lung tissue. There was blood-stained ascitic fluid but no large intraperitoneal hemorrhage. Blood-stained fluid was also found in the right pleural cavity. I believe this could have extended through the diaphragm from the abdomen. There were no old infarcts in the lung to suggest previous attacks of embolism before the relatively terminal one. Other findings were more or less coincidental and certainly not very important. There were many diverticula in the sigmoid and evidence of slight inflammation about some of them. It was evident from reading the protocol that the prosector was in some doubt, from the gross findings, whether to call the liver cirrhotic or not. It showed a very severe grade of passive congestion and was perhaps on the borderline of what could be called a cardiac cirrhosis, but I do not think the microscopical examination supports the diagnosis. I would not call it a cirrhosis.

Dr. Alfred Kranes: Was there anything wrong with the kidneys?

Dr. Mallory: Only a severe grade of passive congestion, evidently secondary to the heart lesion. I do not believe the kidneys were responsible for the acidosis.

Dr. Bernard M. Jacobson: Do you think that episode of pulmonary embolism could have been prevented if she had been given Dicumarol from the beginning?

Dr. Mallory: I am sure I do not know the answer to that. I do not think the evidence is entirely convincing that either the use of Dicumarol or the ligation of leg veins can be counted on to prevent pulmonary emboli.[2, 3]

Dr. Palmer: I shall give up slowly. Could you say that a degree of profound shock could have been caused by this degree of acidosis produced by the treatment given? Could you say it could not have been the explanation?

Dr. Mallory: No; I cannot make a post-mortem diagnosis of acidosis or, in fact, of shock. She may well have had both. How important they were I do not believe myself capable of saying.

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CASE 37142

Presentation of Case

First admission. A sixty-nine-year-old woman entered the hospital because of vaginal bleeding.

The patient had her menarche at the age of 12 and had rather profuse five-day periods at twenty-one-day intervals until the age of 53, when she underwent an uneventful menopause. She had had two normal pregnancies at 19 and 24 years of age and one miscarriage. After her menopause she had no vaginal discharge until two months before admission, when she began to notice pinkish staining and occasional thick yellow exudate. She also noted episodic lower-abdominal discomfort and feelings of pelvic pressure, which were spontaneously relieved by a gush of discharge. One month before admission she presented herself as an out patient because of left-lower-quadrant tenderness and dyspareunia. Pelvic examination at this time revealed an atrophic vagina and a well epithelialized cervix that stained poorly with Schiller's solution. A small, soft, rounded, movable, nontender mass was palpable in the left fornix. Two vaginal smears contained cells that were strongly suggestive of carcinoma. Multiple biopsies of the cervix were reported as chronic cervicitis, and an attempt to obtain an endometrial biopsy was unsuccessful. Hospital admission was advised.

From the ages of 8 to 53 she had epileptic attacks that after the menarche occurred at the time of her periods and ceased with her menopause. Eight years before admission she was found to have hypertension, and since then she had noted exertional dyspnea, orthopnea and rare ankle edema. Four years before admission an electrocardiogram, taken because of a prolonged fainting attack, showed a complete heart block. For three years previously she had had anginal chest pain. The stools had been very dark on occasion for two years before entry, but she had noted no change in bowel habits.

On physical examination the chest was clear. The apical pulse rate was 42, with occasional premature

systoles. The heart was enlarged to percussion and the sounds were distant and of poor quality. A Grade II systolic murmur was heard at the apex. The liver and spleen were not palpable. Pelvic examination performed under anesthesia revealed a multiparous introitus and well supported perineum. The cervix was clean, firm and of normal size. The uterus could not be felt through the obese abdomen but was freely movable. The adnexa were not palpable and the vaults were empty.

The temperature and respirations were normal. The blood pressure was 220 systolic, 110 diastolic.

Examinations of the blood, urine and stools showed no abnormality. A chest film demonstrated clear lung fields and moderate enlargement of the left ventricle. A gastrointestinal series revealed a small hiatus hernia and a barium-enema examination disclosed a single diverticulum in the midsigmoid, with some adjacent narrowing compatible with an inflammatory process outside the bowel. An electrocardiogram showed complete heart block, with an idioventricular rhythm. A third vaginal smear contained cells suggestive of adenocarcinoma.

The patient was digitalized and put on a low-salt diet. On the third hospital day a dilatation and curettage was performed under ethylene anesthesia. The uterine sound was passed for a distance of 8 cm. and the cavity thoroughly curetted, but only one small piece of tissue could be obtained, which was reported as atrophic endometrium. Two cervical biopsies taken at the same time showed chronic cervicitis. The patient was discharged in good condition, to be followed in the Out Patient Department.

Second admission (five and a half months later). Two months after discharge a mass was again felt in the left vault. It seemed to have increased in size since it was first detected and to have become fixed to the uterus and left pelvic wall. A fourth vaginal smear was reported as positive for malignant cells. The vaginal discharge gradually increased in amount so that the patient soiled a pad a day with dirty-brown, whitish or greenish material. She also noted an increase in urinary frequency to 6 to 9 times a day, with 3-times nocturia. The patient continued to take maintenance doses of digitalis but had no change in the symptoms of cardiac insufficiency. The second hospital admission was delayed because of her daughter's death from carcinoma of the breast.

When she returned to the hospital physical examination and laboratory findings were generally unchanged. On the fourth day an operation was performed.

Differential Diagnosis

Dr. Langdon Parsons*: With this two-month history of vaginal bleeding that occurred sixteen years after the menopause, I certainly must rule out any possibility of carcinoma of the endometrium. What evidence is there for this diagnosis? In the first place, there is the prolonged menstrual history — she began having periods at the age of 12 years and continued to the age of 53 years, some four or five years longer than the average woman. Women who develop carcinoma of the endometrium are very likely to have this kind of history. She also had some postmenopausal bleeding, although it did not amount to very much. Bleeding with carcinoma does not have to be continuous but may be spotty and may occur intermittently. The mere fact that she had only a pinkish staining does not rule out carcinoma of the endometrium. In addition, this patient was obese and had hypertension. These are common findings in patients who have carcinoma of the endometrium — perhaps above the average expectancy for patients of that age. They also may have associated pelvic disease — inflammation, an ovarian cyst and so forth. There seems to be something about the constitutional make-up of the patient who develops carcinoma of the endometrium that makes her also develop other pelvic disease more frequently than one would expect.

Carcinoma of the cervix is also a possibility and is so much more common than carcinoma of the endometrium that it should be considered as the cause of any postmenopausal bleeding. Repeated biopsies were done in the Out Patient Department and all showed chronic cervicitis. Were they taken from the external portion of the cervix or the internal portion? This patient could have presented a perfectly normal cervix and still have had disease within the endocervix.

Dr. Benjamin Castleman: The endocervix was not biopsied.

Dr. Parsons: On the other hand, she did have a dilatation and curettage, which the investigator described as very thorough, and no carcinoma of the endocervix was encountered. She had positive vaginal smears, one of which showed adenocarcinoma, so that it is possible that a carcinoma of the endocervix may have been missed. With no evidence of carcinoma of the cervix, endocervix or vagina, I have to suspect even further the possibility of carcinoma of the endometrium.

There are, however, several observations that argue against carcinoma of the endometrium. Although the patients who develop carcinoma of the endometrium have a prolonged menstrual life, as this patient did, they also tend to have throughout life an abnormal menstrual bleeding pattern; about 20 per cent will have had a previous dilatation and curettage for abnormal bleeding. This patient had no such history; she had a perfectly normal menstrual history and menopause. At the time of the menopause there were no untoward symptoms, no profuse bleeding and no prolonged bleeding. Except for the epilepsy associated with

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the periods, there was nothing unusual about the menstrual history. That makes one wonder if she was a suitable candidate to develop carcinoma of the endometrium.

Another factor is that this patient was said to have an atrophic vaginal epithelium. Surprisingly enough, she probably came into the hospital because of dyspareunia at the age of 69 years — and yet she was said to have atrophic vaginal epithelium! In a patient who has carcinoma of the endometrium, the vaginal epithelium is likely to be blue and moist, reflecting the influence of estrogen production without the balancing progesterone, not of the parchment-like atrophic type. It is rare to see carcinoma of the endometrium develop in a patient with atrophic vaginal epithelium. There was still further suggestion that there was a lack of estrogen stimulation, in that the endometrium was also atrophic. I think I can say that both carcinoma of the endometrium and a functioning ovarian tumor — carcinoma of the ovary or a granulosa-cell tumor — are unlikely, because if she were bleeding from one of them she would have had some stimulation of the uterine mucosa. When bleeding occurs with a functioning ovarian tumor it is the result of stimulation of the endometrium, and this patient had an atrophic endometrium.

I think the strongest argument against carcinoma of the endometrium is the fact that no curettings were obtained at a thorough curettage. Should I forget the diagnosis of carcinoma of the endometrium because of the negative curettage? I think not. A dilatation and curettage is not 100 per cent accurate. Although we believe that after a negative dilatation and curettage the patient cannot have a carcinoma of the endometrium, we have been fooled time and again. Carcinoma lurking in one corner of the uterus or at the base of a flat polyp may be missed even though the curettage is very thorough. Such a patient, particularly with a history of repeated positive vaginal smears, should still be considered to have carcinoma if there is any subsequent bleeding.

There are other sources of postmenopausal bleeding. Spotting may occur with hypertension, with atrophic endometrium or with polyps. If it were not for the positive smear I would postulate that the vaginal bleeding might have come from the hypertension. Remember, also, that she had a mass in the left lower quadrant that tended to press on and narrow the lumen of the sigmoid, possibly a single diverticulum in the midsigmoid. She may have had bleeding from hypertension and had coincidentally a mass secondary to the perforation of a diverticulum with a pelvic abscess. She may have had carcinoma of the sigmoid attached to the uterus with a uterosigmoid fistula and may have discharged material into the uterus. In this way the positive vaginal smears could be explained.

Dr. Allen G. Brailey: How often do patients bleed from hypertension?

Dr. Parsons: I think it is not uncommon — I would say about 15 per cent — and when a dilatation and curettage is done all that is found is atrophic endometrium or no endometrium. Why, I do not know; perhaps it is on the same basis as the epistaxis.

Dr. Stanley M. Wyman: There is nothing to add to the description of the films of the chest. The heart is enlarged in the region of the left ventricle. The aorta is quite tortuous and calcified, in keeping with the known hypertension. The chest, and particularly the heart, show no change at the time of the second examination five months later. The examination of the upper gastrointestinal tract shows the small hiatus hernia, but the stomach and duodenum are not remarkable otherwise. The films of the barium-enema examination show unusual narrowing of the sigmoid for a rather long distance. There is one diverticulum in the sigmoid. From the information at hand I am unable to make a specific diagnosis. I do not see any frank tumor. The process in the sigmoid appears to be quite diffuse.

Dr. Parsons: You hold to the pressure of an extrinsic mass as a cause of the sigmoid defect?

Dr. Wyman: There is a soft-tissue fullness in the left lower pelvis, but that could represent bladder.

Dr. Parsons: There is no lateral view of the barium-enema examination that might show displacement of the sigmoid?

Dr. Wyman: No.

Dr. Parsons: I think I shall go back to the history and look for further leads. There is a significant statement that the patient had episodes of lower-abdominal distress and a feeling of pelvic pressure, which were relieved by a sudden discharge from the uterus of white-greenish material and blood; the discharge later became continuous. It does not say whether or not there was pus, but a white-greenish kind of material might well have been pus. She also noted tenderness in the left lower quadrant, and the mass was palpated there. Two months later there was a mass, that increased in size, fixed to the uterus and lateral wall of the pelvis. Finally, she had urinary symptoms — frequency, pressure and nocturia. The discharge continued and increased in amount.

I am still trying to explain the positive vaginal smear and the negative curettage and biopsy. One possibility is a rare pelvic cancer. The history fits this cancer so completely that I believe I have to consider the possibility of carcinoma of the fallopian tube. Characteristically the history closely resembles that of pelvic inflammation. These patients have low abdominal distress and a palpable mass and may have chills and fever. The curious thing is that every now and then these patients will "gush out" a good deal of blood and

have relief from the symptoms. If they are operated on, unilateral disease that looks like a large hydrosalpinx is found; the diagnosis is unsuspected, and only one tube is removed. The results are very poor. Fairly typically in carcinoma of the tube the fimbriated ends close and the tube becomes distorted into an enormous retort-shaped thin-walled mass that may extrude its contents into the uterus and vagina. I can explain the findings of a negative endometrial biopsy and a positive vaginal smear by carcinoma of the fallopian tube. I shall rest with this diagnosis.

Clinical Diagnosis

Carcinoma of the fallopian tube.

Dr. Parsons' Diagnosis

Carcinoma of the fallopian tube.

Anatomical Diagnosis

Carcinoma of the fallopian tube with extension to endometrium and ovary.

Pathological Discussion

Dr. Robert Shaw: Dr. Joe V. Meigs explored this patient and found a left tubo-ovarian mass that was adherent to the cul-de-sac and left posterior pelvic peritoneum. The right tube was normal and the right ovary very small and atrophic. He was able to remove all the grossly diseased tissue by doing a total hysterectomy and bilateral salpingo-oöphorectomy and excising the cul-de-sac and a portion of the peritoneum in the left pelvis overlying the ureter. There was no involvement of the sigmoid by the mass.

Dr. Castleman: Was it adherent to the sigmoid?

Dr. Shaw: No.

Dr. Castleman: The right tube was normal. The left tube was retort-like and markedly distended, as Dr. Parsons predicted. In the tube was a large papillary granular mass that was obviously carcinoma. The mass apparently involved the entire ovary, and on microscopical section there was no remaining ovarian tissue that we could find. We did find soft, diffuse, abundant endometrium, and we wondered why it was so difficult to get material at the dilatation and curettage. Microscopical examination showed that this was also papillary adenocarcinoma but limited to the surface; it had not invaded the basal layer of the endometrium, so that I feel fairly certain that it was not a primary tumor of the endometrium. There was some endometrial involvement in the endocervix down close to the external os, which I am sure was a metastasis from the tubal tumor. Within the tumor there were many foci of calcification characteristic of the psammoma bodies that so often are seen in papillary carcinomas of the ovary, so that it is possible that this was a primary tumor of the ovary. I see no reason, however, that they may not be seen in a primary tumor of the fallopian tube as well. We looked at the endometrial biopsy again and found that it showed endometrium of the lower uterine segment rather than true endometrium. I think the surgeons never reached the fundus of the uterus.

Dr. Shaw: Is it not possible that there had been spread of the tumor to the endometrium since the time of curettage six months before? I think an 8-cm. sounding of the uterine cavity must have been in the fundus.

Dr. Castleman: Yes. It is quite possible that the tumor had extended into the endometrium between the two operations.

Dr. Parsons: It is interesting that three of the few cases that we have had in this hospital have gone through the same kind of history and actually developed the disease under observation.

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A GOOD RECIPE

THE organization of a new district medical society — Middlesex West — as a component part of the Massachusetts Medical Society has been effected with propriety and duly recorded in these columns.

The event was marked by a maximum of sincerity and a minimum of pomp and circumstance; it was in addition the occasion for a forthright declaration by the secretary of the parent society of the obligations that the fellows of every district should assume. The essence of Dr. Gallupe's advice was contained in his "recipe" for a good district medical society — a recipe of action containing ten positive ingredients.

These specific charges are, without elaboration, as follows:

I. Contact your members who have not paid the American Medical Association dues for 1950, and persuade them that this is a duty of paramount importance.

II. Campaign to increase the membership of your district society to include every eligible physician.

III. See that your councilors discuss the advance information to councilors before the meeting of the Executive Committee, and again before the meeting of the Council.

IV. Make it possible for every registered physician in the district to care for his patients in an approved hospital. This is a public necessity; an act of justice to the physician who is entitled by law to practice medicine, and to his patients.

V. Let the public know that good medical care can be obtained regardless of the patient's ability to pay.

VI. So organize the professional facilities of your district that the services of a physician are available every hour in every day.

VII. Discuss the fee with the patient before the first bill is sent.

VIII. Put service before financial gain.

IX. Study the proceedings of the House of Delegates of the American Medical Association and the Council of the Massachusetts Medical Society as they appear in your journals.

X. Know the Code of Ethics.

A literal acceptance of Dr. Gallupe's remarks will go far toward the establishment of good relations between the profession and the public.

NEW LAMPS FOR OLD

THE Eye-Bank for Sight Restoration, of New York, with which the Boston Eye-Bank is affiliated, has recently issued its fifth annual report.

When the bank was established, so few years ago, no more than twelve or fifteen surgeons in the country were performing corneal-graft operations. At the present time more than a hundred surgeons are operating regularly, and many thousand persons, now blind, are potential candidates for their skill and for the eyes that are coming in increasing numbers to the bank and its affiliated stations.

Already over 2000 eyes that were bequeathed by their living owners have been delivered, with 155 hospitals stimulating donor interest and co-operating in the prompt dispatching of eyes to their destinations.

In the matter of transportation, also, teamwork has been developed to a high degree, for only forty-eight hours may elapse between the death of the donor and the grafting of the corneal tissue in the eye of the recipient. In this race against time the airlines of the country and the Motor Transport Corps of the Red Cross have co-operated with split-second precision — "Neither snow, nor rain, nor heat, nor darkness, are permitted to obstruct their speed" when on this errand.

NEW ENGLAND COUNCIL

AN ANNOUNCEMENT of the spring meeting of the Council of the New England State Medical Societies appears elsewhere in this issue of the *Journal*.

This meeting, which has been an annual affair for several years, should be a matter of considerable importance in New England medical circles. Unfortunately, it has been little publicized, and the fellows of the various societies, accustomed to thinking of the Council only in terms of the Postgraduate Assembly, which it sponsors each fall, are generally unaware of the fact that they will be welcomed also at the other meetings.

On Sunday, April 15, the meeting will be called to order at 2:30 p.m. at the Copley Plaza Hotel. The main part of the program will be devoted to short discussions of various topics by the presidents of the six societies and will be followed by a dinner, with President Albert N. Jorgensen of the University of Connecticut as the principal speaker.

On what have seemed to be suitable occasions, the desirability of solidarity among the medical societies of New England has been stressed in the *Journal*. This business is the concern of all. Each society's representatives on the Council deserve the interested and active support of their medical colleagues.

THE GOOD SAMARITAN

THE House of the Good Samaritan in Boston, an institution that has always been held in the highest regard in this conservative medical community, was originally a hospital for the care of convalescent women patients referred from the Massachusetts General Hospital and later was used for the care of sufferers from certain protracted or chronic illnesses. These fell into two general groups: patients with incurable cancer, who were admitted for terminal care, and children with chronic or relapsing rheumatic fever, for which there was no specific treatment.

For over twenty years the facilities of the hospital have been devoted to patients in the second group, so that its name is now identified only with rheumatic fever and rheumatic heart disease.

More and more, however, as specific measures have been developed for the control of acute rheumatic fever, attention has turned to this phase of the disease. One of the mechanisms by which this control may be effected is the prevention of the spread of infection with beta-hemolytic streptococcus, methods for which have been developed at the "Good Samaritan."

Dr. Howard B. Sprague, president of the American Heart Association and chief of staff of the House of the Good Samaritan, draws attention to this progress in a letter to the editor, published elsewhere in this issue of the *Journal*, and reminds physicians that beds are available in the hospital for the early care of young patients with acute rheumatic fever.

Dr. Wm. Turner, of New York city, has petitioned the Legislature of the State to pass a law making the use of the lancet in diseases a penal offense.

Boston M. & S. J., *April 9, 1851*

MASSACHUSETTS DEPARTMENT OF PUBLIC HEALTH

DISTRIBUTION OF FLUID TETANUS TOXOID

Distribution figures from the Division of Biologic Laboratories show that during 1950 enough fluid tetanus toxoid was distributed to give 14,000 people complete primary immunizations. Since distribution first began, in July, 1949, over 18,000

such immunizations have gone into distribution. It is gratifying to see the increasingly wide usage of tetanus toxoid. These figures do not include the tetanus toxoid present in other biologic products that are used in the preschool and school age groups in the State, nor do they include commercial material used. It is presumed that the majority of immunizations using fluid toxoid are booster doses or primary immunizations of adults. The Laboratory has had many inquiries during the year, particularly from industrial plants in which immunization of personnel is planned.

Production of tetanus toxoid at the Forest Hills Laboratory has increased somewhat during the year, and it is felt that an orderly increase in immunizations of perhaps 50 per cent over 1950 could be met in 1951. As tetanus toxoid has almost entirely supplanted tetanus antitoxin in the armed forces, it is believed that immunizing a civilian population in such a way is a desirable accomplishment, especially in view of the threat of modern war. This would aid in the conservation of tetanus antitoxin for use in those injuries in which the threat of overwhelming tetanus infection exists.

COMBINED DIPHTHERIA-TETANUS IMMUNIZATION

The Department believes that due to the value of immunizations in which tetanus toxoid has been combined with other agents it is advisable to use such products wherever possible. The Biologic Laboratories are therefore temporarily suspending the manufacture of fluid diphtheria toxoid. Orders for fluid purified diphtheria toxoid are filled by providing diphtheria-tetanus toxoid aluminum phosphate precipitated on the basis of the number of complete human immunizations ordered. For example, two 20-cc. vials ordered would immunize 16 persons; the order would be filled by supplying four 7.5-cc. vials of the diphtheria-tetanus precipitated material, which would be sufficient to give 20 complete immunizations of three 0.5-cc. injections per person.

In regard to the shift from fluid to precipitated products the importance of giving alum-precipitated biologics *intramuscularly* should be emphasized, especially to those physicians who have not used them previously.

The added immunity obtained, ten times that of fluid toxoid, is the principal advantage derived from the use of multiple antigens to which aluminum has been added in one form or another.

JAMES A. MCCOMB, D.V.M.

MISCELLANY

ASSOCIATION OF INDUSTRIAL MEDICAL OFFICERS

The Association of Industrial Medical Officers of Great Britain is planning the quarterly publication of the transactions of the Association.

Communications concerning the new journal should be addressed to Dr. J. A. A. Mekelburg, Hon. Secretary, Peek Frean & Co., Ltd., Keetons Road, Bermondsey, London, S. E. 16, England.

CORRESPONDENCE

THE HOUSE OF THE GOOD SAMARITAN

To the Editor: The House of the Good Samaritan in Boston has been devoted exclusively to the care of patients with rheumatic fever and rheumatic heart disease for more than twenty years. In concentrating on this very specialized task, this hospital has rendered service to over 3000 patients. It has also been a pioneer in the newer methods of treatment and prevention. Indeed, the standards generally used for the diagnosis of rheumatic fever were developed in this institution.

Although the House of the Good Samaritan has cared for patients in the chronic stage of the disease, it may not be generally known that beds are also available for the care of patients with acute rheumatic fever. This has become particularly important because methods have been developed in this institution for the prevention of spread of infection with beta-hemolytic streptococcus, which on the wards of general hospitals frequently precipitates recurrences of the disease. It is therefore advisable to admit patients to this institution as early in the disease as possible. There are facilities for the care of children of both sexes to midadolescence, and for adult females. The newer therapeutic agents and methods of treatment are also available for patients when indicated.

The House of the Good Samaritan is now prepared to admit, on short notice, patients referred for diagnosis or treatment by physicians and by other hospitals in New England. Admission can be arranged by communicating directly with the admitting officer at the House of the Good Samaritan, 25 Binney Street, Boston 15, Massachusetts, BEacon 2-3207.

HOWARD B. SPRAGUE, M.D.
Chief of Staff

Brookline, Massachusetts

ACTH AND TUBERCULOSIS

To the Editor: Notwithstanding the marvels that ACTH is destined to produce in some of the greatest medical problems, it may be taken as a foregone conclusion that it will prove useless or harmful if applied to the treatment of pulmonary tuberculosis. This statement is based on the fact that the work done with ACTH to date shows that it increases the urinary excretion of purines while leaving stationary or decreasing the excretion of creatinine. Such a condition renders more favourable growth of the tubercle bacillus in persons who are actively infected with this organism.

The turn for the better in the mortality rate per 100,000 came to England and Wales almost a century ago. In 1838 the rate was 378 and in 1853 it was 303, but by 1863 it was down to 251 for males and females of all ages. Nothing had occurred in the medical world during that decade to justify that favourable change in the mortality rate. Something had, however, taken place in the National Commercial Policy. The excise duty had been abolished on soap and the import duty on tea had been reduced by two shillings per pound. This last change had increased the consumption of tea from one pound per capita per year to almost three pounds.

The incidence of pulmonary tuberculosis followed closely upon events that increased the creatine of the blood. Three conditions became notorious as the precursors of an outbreak of the disease, namely, prolonged muscular exercise, maternity and puberty. Since figures are not only becoming scarce, at the present time, but are likely to have been modi-

fied by various agencies at work and by our more favourable living conditions, the age and sex incidence of the mortality from this disease in England and Wales for 1864 is given for a time when it was still the leading cause of death.

Age	Male	Female
5–10	511	593
10–15	720	1189
15–20	2229	3220
20–25	3508	3958
25–35	6051	7379
35–45	4924	5014
45–55	3453	2669

Children excrete creatine up to the age of puberty. It will be seen from the above figures that during that period of life tuberculosis was at its minimum. At that time of life glycerophosphate, the by-product of muscular activity, finds an outlet in bone development. So, with these two substances taken care of — creatine by excretion and glycerophosphate by internal metabolism — two potent sources of culture media for the tubercle bacillus are eliminated; therefore children were comparatively immune from phthisis, even in the bad old days.

With regard to prolonged muscular exertion, during the Industrial Revolution, when a 16-hour working day was common, the reverse of the conditions of childhood was the case. With the exhaustion of muscular purine bases creatine production, as a source of phosphate energy in a quicker form, became a part of the normal metabolism of such workers. The by-product glycerophosphate, not required for bone development to the same extent after puberty, sought an exit by way of the lung tissue. The increased production of creatine caused a delay in choline formation, since these substances compete for the possession of methyl groups. A depressed choline supply interfered with the formation of lecithin and other phospholipids, with a consequent disarrangement in the metabolism of food fat. This latter commodity was notoriously bad when it appeared on the tables of the poor or in cook-shops, a century ago. The result of phospholipid dystrophy was a further demand on the phosphate united with the purine bases, particularly adenine.

In normal subjects this last substance recovers its phosphate stores, as attested by the retention of uric acid during fat absorption. But with the tuberculous this is not always the case. Parkinson, as long ago as 1906, showed, with reference to patients at the Gateforth sanitarium, that the urinary excretion of purines was 57 per cent greater in tuberculous than in normal persons, when both groups were on a purine-free diet. From Dehaussy's work with tuberculous rabbits, as quoted by Wells, it seems that the bacillus in question secretes some substance that is capable of stimulating the kidney, in man and in some mammals, to increase the excretion of purines. This seems more reasonable when it is recalled that purines and uric acid are two forms of nitrogen that cannot be used in the culture of tubercle bacilli, as opposed to creatine, which forms a favourable medium of growth.

It was common knowledge a century ago, when both diseases were at their height, that the gouty were not subject to tuberculosis, and vice versa. It was also common knowledge that the remedies that were applicable to one of these afflictions were contraindicated in the other. Phlebotomy was useful in early phthisis, the prime requisite being a certainty of diagnosis. Its action had more than one channel of operation, but the urinary excretion of creatine, which follows phlebotomy or haemorrhage from accidental source, was a definite factor in the improvement of cases suffering from pulmonary phthisis. Phlebotomy on the other hand was frowned upon as a treatment for gout.

As the importation of tea into England increased, from one half pound per person per year in 1810 to one pound in 1850, to four pounds in 1870 and to six pounds in 1900, so also did the use of butter as a food fat in place of tallow. The export market for soap had much to do with the consumption rise from two pounds of butter per capita per annum in 1870 to eight pounds in 1900. During that thirty years the death rate from tuberculosis had been cut in half, although up to that time no progressive steps had been launched in the wider sense for the treatment of the disease.

It became standard practice for some English midwives to give a cup of tea to their patients as soon as possible after delivery — a time when the blood is very high in creatine and the kidney already overloaded. The work of Bachmann and his associates fully justifies that practice, which was probably initiated by some unsung physician prior to the turn of the century, and before biochemistry had been demoted by bacteriology from the leading role it then held. Bachmann* found that administration of caffeine in sufficient quantity was followed by the excretion of creatine in man. The progress of biochemistry since 1927 has been such that many clinical facts of former days can now be brought out and rationalized in the light of recent discoveries, and although tuberculosis has ceased to be a major medical problem it is well to understand a phenomenon that was recognized by Austin Flint before 1875 and before it was known that glycerin held such an important place in the growth of an organism that was as yet undiscovered. He said: "Pulmonary phthisis in some cases ceases to progress; the regression continues, recovery taking place from an intrinsic tendency that is irrespective of any measures of treatment. . . I have established it by having recorded a series of cases in which recovery took place without medicinal or other treatment and without any material change in habits of life."

The whole of Dr. Flint's statement is correct except the last clause, for his patients had changed their habits of life between the time that he founded the Buffalo Medical School and the time that he penned those lines. The consumption of coffee in the United States had multiplied itself by five during that period, and there is little doubt that Dr. Flint's patients had their quota or perhaps a little more.

It is to be expected that a substance that has solved the unexpected problems that have puzzled modern medicine might be applied to each and all of the conundrums still facing the profession. But it would be wrong to treat pulmonary tuberculosis with ACTH. This latter substance must not be expected to run with the hares and hunt with the hounds. It has relieved gout in a satisfactory way, but all tradition and a long series of clinical analyses have shown that with regard to treatment tuberculosis and gout are as far apart as the poles.

Frank N. Walker, M.D.

Toronto, Canada

*Bachmann, G., Haldi, J., Ensor, C., and Wynn, W. Creatinuria in man following oral administration of caffeine. *Am. J. Physiol.* 138:78-82, 1942.

NATURAL BIRTH AND DEMAND FEEDING

To the Editor: I hesitate to comment on an article on obstetrics by a physician as eminent as Dr. Irving; but I think that both "natural childbirth" and "demand feeding" deserve more serious consideration than he has given them in his review in the January 18 issue of the *Journal*. I am a third-year medical student at Yale, but I have also recently given birth to a baby at the New Haven Hospital under the modified Read program. While in the hospital I stayed in the Rooming-In unit, where the mothers are encouraged in the correct use of a demand feeding program. Under these circumstances I hope that I am more qualified to speak than I might otherwise be.

Dr. Irving has probably put a fair evaluation on Dr. Read's success in saving mothers from the pain of labor when he says that many of these patients wouldn't have experienced much pain under any circumstances. He fails, however, to draw the natural conclusion of his observation, which is: Since anesthetics in obstetrics are never used without some hazard, these fortunate women and their babies should not be subjected unnecessarily to the risk involved. The service at the New Haven Hospital is dedicated to the idea that each prospective mother is an individual, and an effort is made to adjust her analgesia and anesthesia to her particular needs and desires. In addition, many women derive much joy and satisfaction from participating actively and consciously in the birth of their children. It seems worth while to help them achieve this end. It has been found that in the majority of cases this can be done without much discomfort for the mother. I believe that this natural and individual method of treating the patient is considered by many to be an important step in modern obstetrics.

Now to turn to the feeding of a newborn infant. Being in the midst of this problem, which seems to give rise to much debate, I think I am safe in guessing that it has been a long time since Dr. Irving took care of a very young infant on a twenty-four-hour basis, if ever. For a very small baby

there can be no question of discipline, as he suggests. The baby has no will, no reasoning and certainly no wiles. You might as well spank him for wetting his pants as to let him scream feverishly because his appetite doesn't coincide with the clock. Demand feeding is certainly the only normal equitable arrangement for mother and baby. With tender, loving care he learns to trust his mother and to face new situations without anxiety. There is time enough to begin molding his character.

(Mrs. W. R.) SIEGRIED A. CENTERWALL
New Haven, Connecticut

LAW AND ORDER

To the Editor: In November, 1948, the voters of Massachusetts had an opportunity to go to the polls and alter the antiquated and inept Chapter 272 of the General Laws of the Commonwealth entitled "Crimes against chastity, morality, decency, and good order" by voting Yes on Referendum Question No. 4. Passage of this referendum would have made it no longer an offense to advertise or give information on the procurement of means for prevention of pregnancy or conception in those married women adjudged by registered physicians to be jeopardizing their lives or health by further pregnancies.

The final count on Question 4 was 806,829 Yes; 1,085,350 No; and 263,168 blanks. Thus it stands — that any physician imparting any kind of information or guidance toward the prevention of pregnancy under any circumstance is liable to "punishment in state prison for not more than five years, or in jail or the house of correction for not more than two and one half years, or by a fine of not less than one hundred nor more than one thousand dollars."

Many a law, even as silly and ill-advised as the above, has been successfully erased from the statutes by studied obedience of the constituents. Therefore, let each physician place a copy of Chapter 272, Sections 20 and 21, of the General Laws in a conspicuous place in his office, where his patients, especially those seeking birth-spacing information and advice, may view the law in its completeness. Mutual understanding will be accomplished, the physician will not be a lawbreaker and many a new crusader for a just cause will have been born.

H. H. HAMILTON, M.D.
Plymouth, Massachusetts

HOSPITAL EPIDEMIOLOGY

To the Editor: Being a newcomer in this area, and a new but regular reader of the *New England Journal of Medicine*, I wish to express my appreciation of the clear and forthright manner in which your scientific articles and editorials are presented.

Specifically, I was very favorably impressed with the report of the outbreak of infections with *Salmonella newington* in one of the Boston hospitals, which appeared in the February 15, 1951, issue of the *Journal*. I was especially impressed by the frankness with which the authors discussed their lack of information on the sources of infection and the reasons they gave to explain the difficulties they faced in the gathering of epidemiologic information that they sorely needed, if they were to bring the spread of infection under control or to prevent another outbreak of a similar or more severe nature at some future time.

Not only were they faced with a highly complex problem of tracing the many food sources supplying the hospital (which they dropped without investigation frankly because "this aspect did not promise to be very fruitful"), but they faced the even more vexing situation of not being able to secure sufficient co-operation from those hospital employees coming into contact with food (only "half the food handlers") to obtain enough fecal and urine specimens for conclusive cultural studies. I was mentally contrasting this "lack of co-operation" among hospital employees to that found among the employees of commercial eating places when similar outbreaks have been traced to them in recent years, and was wondering how great a part might be played by effective food-handler education, when my eye caught this statement toward the end of the article: "Hospital food handlers, like those in public eating places, should be under some control and supervision by public-health authorities."

Realizing that the establishment of effective hospital epidemiologic services, on a professional par with internal medicine, surgery, radiology, psychiatry, obstetrics and so forth constituted a bit more than simply bringing them "under some control and supervision by public-health authorities," I thought of some of the legal aspects, the administrative problems, various factors involved in employee and staff education, professional consultation between health department and hospital staffs and other aspects of such a team approach to the problem as the authors' reference to "supervision by public-health authorities" implied.

At about this stage of my thinking I came to your editorial, in the same issue of the *Journal*, entitled "Nosocomial Gastroenteritis," in which you discussed the same article, and outlined a possible plan of approach to hospital epidemiology that anticipated many of the questions that would need to be answered before any such plan could be put into effect. Your conclusions and recommendations seem to me to be so sound from both the medical and the public-health point of view and so practical on the whole as to deserve adoption and a fair trial.

FRED MAYES, M.D.
Director of Public Health
Brookline, Massachusetts

COMMENT ON ADOPTION PROCEDURES

To the Editor: The editorial on the law relating to adoption brings to my mind the complaint of several parents who have adopted children in this state, namely, that the social worker sent out to investigate the home is usually insistent upon identifying the source from which the child comes.

It has been my experience that parents who are about to adopt a child generally wish to know nothing concerning the child's parent or parents, and do not want their name or location known to the lawful parents, believing that a complete cleavage makes for greater happiness on the part of both parties. In one instance in which the adopting parents, having been warned, told the social worker that they did not wish to know anything about the child's parentage, the social worker went to the child's crib and said, "James, if you ever want to know anything about your parents, you come and see me. I know all about it."

I am wondering if the interest that the state takes in adoptions should not be extended to an interest in those who "make the appropriate inquiries." Could we not, as a society, take some interest in promoting standards for the social workers in the Department of Public Welfare, standards that would relate not only to educational background but also to the wisdom, honesty, and human kindness that should be inherent in such persons?

M. GENE BLACK, M.D.
Holyoke, Massachusetts

CURTAILMENT OF ESSENTIAL SERVICE

To the Editor: I am writing in regard to the statement by the Massachusetts Department of Public Health, published in the December 14 issue of the *Journal*, that announced the restriction of services at the Wassermann Laboratory. This stated that because of a cut in federal appropriations henceforth no complement-fixation tests and no quantitative Hinton tests on blood or spinal-fluid specimens would be run regardless of the specific request of physicians. It was also announced that a new program for determination of total protein on spinal-fluid specimens with positive serologic tests would be shelved indefinitely.

It is considered that these restrictions are indeed serious curtailments of service. Quantitative serologic tests on the blood are generally regarded as extremely important in the proper follow-up of patients treated with penicillin for early syphilis and in the evaluation of possible false positive tests. In the period of seropositivity that follows the penicillin treatment of all patients with seropositive early syphilis, treatment failures can be picked up with quantitative tests (failure of titer to fall, or increase in titer after a preliminary decrease) whereas qualitative tests show no change. Quantitative serologic tests on spinal fluid are very helpful in determining prognosis, exact diagnosis and the effect of treatment in central-nervous-system syphilis. Complement-fixation tests (particularly quantitative tests on spinal fluid)

and total protein determinations on spinal fluid are also generally regarded as essential in the proper management of the disease.

The Executive Committee of the Massachusetts Society for Social Hygiene, on the advice of its physician members, has instructed me to write this letter of protest to the *Journal* and to send copies to Dr. Vlado A. Getting, Massachusetts Commissioner of Health; Dr. Theodore J. Bauer, Chief, Division of Venereal Disease, U. S. Public Health Service; and Dr. Leonard A. Scheele, Surgeon General, U. S. Public Health Service. It was believed that these essential services should be restored and, since federal support seems uncertain, that it would be preferable for State support to be increased to the point where it would cover these services.

It would be particularly unfortunate for essential laboratory services to be curtailed at a time when it seems that progress is being made in the control of syphilis.

WILLIAM L. FLEMING, M.D.
President, Massachusetts Society for Social Hygiene
Boston

DEPRIVATION OF LICENSE

To the Editor: At the meeting of the Board of Registration in Medicine held March 15, it was voted to revoke the registration of Dr. Louis C. Billotte, 63 Bellevue Avenue, Melrose.

ROBERT C. COCHRANE, M.D., *Secretary*
State House
Boston

BOOK REVIEWS

Medical Dictionary; Dictionnaire Médical; Medizinisches Wörterbuch. Editor-in-chief, Emmanuel Veillon, M.D. 8°, cloth, 476 pp. New York: Grune and Stratton, 1950. $18.75.

This work is actually a trilingual medical vocabulary rather than a dictionary in the currently accepted sense, since the words listed are not defined. It consists of a large collection of medical terms in three synoptic columns giving the equivalent words in the respective languages. The volume is divided into three sections, — English–French–German, French–German–English and German–English–French, — each preceded by a list explaining the abbreviations employed. In spite of the high price it should prove useful to those who wish to read the modern medical literature in the three European languages most widely used at present.

R. O'L.

A Primer of Venous Pressure. By George E. Burch, M.D. 8°, cloth, 174 pp., with 170 illustrations. Philadelphia: Lea and Febiger, 1950. $4.00.

This book, though primarily intended for the beginner, will certainly be perused with benefit by anyone interested in the problems of blood flow. Considerations of venous pressure are used to lead the reader through an amazingly extensive review of the nature of blood flow in many physiologic units in the body. The reader is induced to think in concrete terms of the dynamics of the circulation, in both normal and abnormal states. One is reminded of the truth of Lord Kelvin's observation that when one begins to measure natural phenomena, one approaches an understanding of them.

The book is concise, clearly written and profusely illustrated with excellent diagrams. It is recommended for both medical students and physicians.

Principles of Internal Medicine. T. R. Harrison, editor-in-chief. Editors: Paul B. Beeson, M.D., William H. Resnik, M.D., George W. Thorn, M.D., and M. M. Wintrobe, M.D., Ph.D. 4°, cloth, 1590 pp., with 245 illustrations and 114 tables. Philadelphia: Blakiston Company, 1950. $12.00.

This textbook, produced under the direction of a distinguished group of editors, covers the usual aspects of internal medicine by the standard procedure, in that each disease is considered in a separate section. In addition, however, there is a preliminary section devoted to the cardinal manifestations of disease, covering such aspects as pain, weakness, shortness of breath, disturbance of circulation, alterations in weight, fluctuation and electrolyte balance, emotional development, reactions to injury and stress and immune mechanisms. These chapters are excellent and set a high standard of medical writing. The point of view expressed, moreover, is distinctly worth while and is one that is not ordinarily adequately provided in the usual textbook of medicine.

For the rest of the book, less praise can be given. A number of the chapters fail to cover the more recent literature. A report on one disease, a subject of much recent research, only covers the literature of over ten years ago and gives as its only reference another textbook. The author, considering another disease in an adjacent section of the book, gives references, showing his personal interest, to the literature of 1950. This unevenness of presentation militates against the value of this publication and indicates a partial failure in organizing and synthesizing the whole of the material. A few illustrations add little to the value of the book. Occasionally, a chart is found that is helpful, but some of them use abbreviations that only puzzle any except the laboratory expert or teachers in the front rank.

This enormous tome presents something of a problem, for it is not clearly visualized for whom this book was actually written. It will be impressive on the doctor's shelf but somewhat less used in all probability than if it had been issued in two or three handy volumes. Like all textbooks written by leaders in the field of medicine, it contains much of value. It requires, however, a considerable amount of discrimination on the part of the reader to sort out the wheat from the chaff. The chief importance of the book, which is too large and awkward for the practitioner, too uneven in its contents for experts and with varying values of standards for the medical student, lies in the preliminary chapters, which deserve reading and rereading. This section of about five hundred pages should have been issued as a separate publication, leaving the other thousand pages for a two-volume work as a textbook of medicine. If the last thousand pages had never been printed, the loss to the medical profession would have been minor and easily offset by other texts.

Illegitimate Sonnets. By Merrill Moore, M.D. 8°, cloth, 125 pp. New York: Twayne Publishers, Inc., 1950. $2.75.

In his latest and best book of sonnets Dr. Moore firmly consolidates his position as one of America's leading avocational poets.

This book, in the opinion of the reviewer, is much superior to the originally published "thousand"; it is in a class with, but better than, the book of Clinical Sonnets that preceded it.

Tastes in poetry vary from complete indifference to idolatrous worship of the rhythm of formal meter and the finality of the perfect rhyme. The average appreciation of verse includes the requirement that substance be combined with form.

Merrill Moore now finds, as he planishes his lines, that he cannot help beating out measures with the tapping of his hammer.

Take, for example, the spiders in the empty house:

> With nothing, out of nothing, they had built
> A fabulous community of thread,
> Waving and spacious, planned as far ahead
> As any modern city, serving all
> The spiders living on the dusty wall,
> Miraculously watered, sheltered, fed.

J. G.

The Abnormal Pneumoencephalogram. By Leo M. Davidoff, M.D., and Bernard S. Epstein, M.D. 4°, cloth, 506 pp., with 696 illustrations. Philadelphia: Lea and Febiger, 1950. $15.00.

This long-awaited publication is a companion to a previous volume entitled *The Normal Encephalogram.* The first book was largely the product of Dr. Cornelius G. Dyke, who died in 1943 at the height of his career. Fortunately, the present authors have continued the work in the spirit of Dr. Dyke, and the volume upholds in every aspect the high standard set by the first volume. In Part I, which deals with tumors of the brain, there are excellent descriptions of the classic types of tumor and their effect on the skull and its contents

as disclosed by the roentgen ray. The tumors considered are not only neoplasms but also non-neoplastic tumors and conditions such as subdural hematoma, aneurysms and cerebral hemorrhage and thrombosis. Part II deals with non-tumorous lesions of the brain such as cerebral atrophy, platybasia, arachnoiditis, congenital malformations, serous meningitis and rare infections. The book will be an indispensable volume for every roentgenologist, neurologist, neurosurgeon and others who deal with the disorders of the nervous system. The pictures are exceptionally clear and profuse in number; the bibliography is excellent, and there is an adequate index. The book may be considered the outstanding contribution at the present time to its field of medicine.

Pathology in General Surgery. By Paul W. Schafer, M.D. 4°, cloth, 581 pp., with 495 plates. Chicago: University of Chicago Press, 1950. $17.50.

The integration of pathology with surgery is of the utmost importance. This book, written by a surgeon who appreciates the need and value of such integration, emphasizes clinicopathological correlations.

About half the pages of the book contain concise summaries of the pathological and clinical aspects of various surgical diseases. Interspersed appropriately among the summaries, the other pages are filled with color photographs or reproductions of x-ray films illustrating the pathology of the disease under discussion. The book is, as the title implies, for the general surgeon. There is little or no discussion of orthopedic, gynecologic, genitourinary, dermatologic or central-nervous-system pathology. On the other hand, there is a disproportionately large section on diseases of the chest.

The outstanding feature of the book is the quality of the illustrations. Gross photographs, all in color, are remarkable for their clarity. This is true as well of the photomicrographs, which are also in color and which have been made from well stained specimens. The selection of material to illustrate the different pathologic processes is excellent. Black and white reproductions of x-ray films have been used to good advantage to supplement other photographs.

The comments and summaries, interspersed between the photographs, are a mixture of diagnosis, pathology, treatment and prognosis. Although informative and accurate they are, in many instances, so brief that they resemble expanded captions.

The brevity of the discussions and the omission of all but general surgical pathology limit the value of the book for text or reference use, although medical students and pathologists can profit well from the excellent photographs. It is a useful supplement to the library of a physician or surgeon rather than a replacement for standard works on pathology or surgery. The book should be particularly helpful to the surgeon in reviewing for board examinations and clinicopathological conferences and other purposes.

BOOKS RECEIVED

The receipt of the following books is acknowledged, and this listing must be regarded as a sufficient return for the courtesy of the sender. Books that appear to be of particular interest will be reviewed as space permits. Additional information in regard to all listed books will be gladly furnished on request.

Parkinson's Disease: Advice and aid for sufferers of Parkinson's disease and other physical disabilities. By Walter Buchler, M.D. 12°, paper, 79 pp. London: Walter Buchler, 1950. $1.00. $2.00 cloth.

In this small book Dr. Buchler relates his own experiences as a sufferer from Parkinson's disease.

Water and Salt Depletion. By H. L. Marriott, C.B.E., M.D., F.R.C.P., Middlesex Hospital, London, England. 8°, cloth, 80 pp., with 10 illustrations and 6 tables. Springfield, Illinois: Charles C Thomas, 1950. $2.00.

This small monograph is based on the Croonian lectures, delivered in London in December, 1946. The material has been revised and brought up to date. A list of references is appended to the text.

Clinical Nutrition. Edited by Norman Jolliffe, M.D., F.F. Tisdall, M.D., and Paul R. Cannon, M.D., for the Food and Nutrition Board of the National Research Council. 8°, cloth, 925 pp., with 127 illustrations and 78 tables. New York: Paul B. Hoeber, Inc., Medical Book Department of Harper & Brothers, 1950. $12.00.

This composite work by 36 specialists in their particular fields is divided into three parts: diagnosis of nutritional deficiency; the nutrient elements; and therapy and prevention. There is an appendix containing tables of food values, nutrient sources and dietary patterns. Bibliographies are appended to the various chapters, and there is a good index. The type and printing are excellent, but the use of a filled paper makes the volume too heavy for easy handling; this situation could have been avoided by the use of a lighter paper, especially so because the colored and other special plates are tipped into the signatures, and the few radiographic plates might also have been treated in the same way. The volume is recommended for all medical libraries and should be available to all persons interested in the subject.

A Text-Book of X-Ray Diagnosis. By British authors. In four volumes. Vol. IV. Edited by S. Cochrane Shanks, M.D., F.R.C.P., F.F.R., director, X-Ray Diagnostic Department, University College Hospital, London, and Peter Kerley, M.D., F.R.C.P., F.F.R., D.M.R.E., director, X-Ray Department, Westminster Hospital, and radiologist, Royal Chest Hospital, London. 8°, cloth, 592 pp., with 553 illustrations. Philadelphia: W. B. Saunders Company, 1950. $15.00.

The first edition of this treatise was published in 1938–1939. The text has been revised and brought up to date. The material has increased to such an extent that it has been found necessary to publish the second edition in four volumes. The present volume, which is devoted to the bones and joints and soft tissues, is the joint work of seventeen contributors. Bibliographies are appended to the two main divisions. The printing was done in Great Britain. The treatise should be in all x-ray and orthopedic collections.

Gastritis, Ulkus und Karzinom: Röntgenstudie unter Berücksichtigung formal-genetischer Beziehungen. By Professor Dr. J. Bücher, physician-in-chief, Röntgen-Abteilung des Allgemeinen Krankenhauses Heidberg, Hamburg. 8°, paper, 89 pp. with 82 illustrations. Stuttgart: Georg Thieme, 1950. DM 11.50/$2.75. (Distributed by Grune and Stratton, New York.)

This small monograph discusses gastritis and ulcer and cancer of the stomach. The literature of the last twenty years has been evaluated, and a bibliography concludes the text. There are numerous excellent illustrations, mostly roentgenograms. The publishing is excellent, typical of the best German work before World War I. Monographs of this type provide up-to-date information on specific subjects.

Jan Ingenhousz, Plant Physiologist: With a history of the discovery of photosynthesis. By Howard S. Reed, Ph.D. 4°, paper, 391 pp., with illustrations and frontispiece. Waltham, Massachusetts: Chronica Botanica Company, 1949. $3.00. (*Chronica Botanica*, Vol. 11, Number 5/6.)

In this well written monograph, sections one to twenty-seven of the *Experiments upon Vegetables* (London, 1779) of Ingenhousz are reproduced. Preceding this material are a short biography and a history of photosynthesis. An index concludes the text. The publishing is excellent, and the monograph should be in all collections on the subject.

Treatment in Psychiatry. By Oskar Diethelm, M.D., professor in psychiatry, Cornell University Medical College, and psychiatrist-in-chief, the New York Hospital (Payne Whitney Psychiatric Clinic). Second edition. 8°, cloth, 546 pp. Springfield, Illinois: Charles C Thomas, 1950. $8.50.

The first edition of this book was published in 1936. The author has completely rewritten his text to bring it up to date, including advances in psychotherapeutic methods for adults and children, somatic procedures, therapy directed toward the members of the patient's family and the necessity of a closer relation with other medical disciplines, especially with internal medicine and pediatrics. The final chapter discusses the evaluation of current progress and trends. The text is documented with numerous case histories.

The author deals not only with the psychoses but also with the minor personality reactions of everyday life and with reactions to physical illnesses and handicaps. Lists of selected references are appended to the various chapters. The book should be in all collections on psychiatry.

Einführung in die innere Medizin. Von Dr. Hans Julius Wolf, Ausserplanmässiger Professor für Innere Medizin an der Universität Göttingen, Chefarzt des Städtischen Krankenhauses in Bielefeld, und Leiter der Inneren Abteilung. 8°, cloth, 653 pp., with 73 illustrations. New York: Grune and Stratton, Incorporated, 1949. $6.50.

This typically German clinical treatise, first published in 1941, has been revised to include advances in knowledge since the publication of the previous edition. Material on electrocardiography, blood diseases, liver-function tests and chemotherapy has been added. The work encompasses the whole field of clinical medicine, including the diseases of internal secretions, vitamins, diseases of the muscles, bones and joints, infections and parasitic diseases and poisoning. Emphasis is placed on the clinical picture, diagnosis and treatment. The material is arranged according to the systems and organs of the body. The text is concise and well written. There is a good index, and the publishing is excellent and is typical of pre-war German standards. The book should prove useful to German-reading physicians.

Infrared Radiation Therapy Sources and their Analysis with Scanner. By Leopold Rovner, consulting physicist, Cambridge. 16°, cloth, 34 pp., with illustrations. Springfield, Illinois: Charles C Thomas, 1950. $1.50.

This monograph is based on a lecture delivered by the author at the meeting of the American Congress of Physical Medicine in September, 1946, and on a paper by Rovner, Paul and Nines, published in 1947.

Proctology in General Practice. By J. Peerman Nesselrod, M.S., M.Sc. (Med.), M.D., associate in surgery, Northwestern University Medical School, and associate surgeon, Division of Proctology, Evanston Hospital, Evanston, Illinois. 8°, cloth, 276 pp., with 64 illustrations. Philadelphia: W. B. Saunders Company, 1950. $6.00.

The author has selected from his wide experience the knowledge he believes should be of value to the general practitioner, medical students and house officers. Diagnostic procedures are presented in considerable detail. Beginning with anatomy and physiology, the whole field of proctology is covered, and special chapters are included on preoperative and postoperative care. The book is well published and should prove useful to those for whom it was written.

Fertility in Marriage: A guide for the childless. By Louis Portnoy, M.D., and Jules Saltman. 8°, cloth, 250 pp. New York: Farrar, Straus and Company, 1950. $3.00.

This is a medical book for the layman and discusses in a popular manner fertility and especially infertility and its treatment.

Lipidoses: Diseases of the cellular lipid metabolism. By Siegfried J. Thannhauser, M.D., Ph.D., associate professor of medicine, Tufts College Medical School, and associate physician-in-chief, Joseph H. Pratt Diagnostic Hospital, Boston. Edited by Henry A. Christian, A.M., M.D., LL.D., Sc.D. (Hon.), M.A.C.P., Hon. F.R.C.P. (Can.), D.S.M. (A.M.A.). 8°, cloth, 595 pp., with 125 illustrations and 51 tables. New York: Oxford University Press, 1950. $12.00.

This comprehensive valuable monograph, first published in the *Oxford Loose-Leaf Medicine*, is now made available separately from the larger reference work that is sold only on a subscription basis. The work is a second edition, revised by the author, to bring the subject up to date. The chapter on xanthomatous biliary cirrhosis has been rewritten, and several chapters extended. The newer literature has been discussed in the various chapters and added to the bibliographies appended to the chapters. The book is well published and should be in all collections on disturbances of metabolism.

Handbook of Bacteriology: For students and practitioners of medicine. By Joseph W. Bigger, M.D., Sc.D. (Dublin), F.R.C.P. (London), F.R.C.P.I., D.P.H., M.R.I.A., professor of bacteriology and preventive medicine, University of Dublin, bacteriologist, Sir Patrick Dun's Hospital and the Royal City of Dublin Hospital, Lieut.-Colonel, Royal Army Medical Corps, examiner, University of Glasgow, National University of Ireland, Queen's University of Belfast and Royal College of Physicians in Ireland. Sixth edition. 12°, cloth, 547 pp., with 109 illustrations. Baltimore: Williams and Wilkins Company, 1950. $4.50.

This handbook is a British book. It was first published in 1925 and has gone through twelve printings of the various editions, speaking well for its popularity. The fifth edition was published in 1939. This sixth edition has been thoroughly revised, and the material brought up to date. Two chapters have been added, and 11 completely rewritten. Two chapters are required for chemotherapy, including penicillin and the sulfonamides. The chapters on immunity, intestinal bacteria and undulant fever have been rewritten, and the chapter on viruses and rickettsias is almost entirely new. The book is well published. The printing was done in Great Britain.

Bacterial Infection: With special reference to dental practice. By J. L. T. Appleton, B.S., D.D.S., Sc.D., professor of bacteriopathology, and dean, Thomas W. Evans Museum and Dental Institute School of Dentistry, University of Pennsylvania. Fourth edition. 8°, cloth, 644 pp., with 108 illustrations and 5 plates, 4 in color. Philadelphia: Lea and Febiger, 1950. $10.00.

This fourth edition of a standard reference book has been thoroughly revised by the author. The extensive bibliography is carried as footnotes to the various pages. The book is well published.

James Lind: Founder of nautical medicine. By Louis H. Roddis, Captain, Medical Corps, United States Navy. 8°, cloth, 177 pp., with 8 illustrations. New York, New York: Henry Schuman, 1950. $3.00.

This biography of a pioneer in tropical medicine is written in narrative style. Emphasis is placed on Lind's important work on scurvy. There is a complete bibliography of the writings of Lind, a chronology of his life and an index. The book should be in all collections on medical history and scurvy.

Atlas of Histologic Diagnosis in Surgical Pathology. By Karl T. Neubuerger, M.D., professor of pathology, University of Colorado School of Medicine, Denver, Colorado. With a section on exfoliative cytology by Walter T. Wikle, B.S., M.S., M.D., assistant professor of pathology, University of Colorado School of Medicine, Denver, Colorado. With photographs by Glenn E. Mills, B.A., M.A., department of visual education, University of Colorado School of Medicine, Denver, Colorado. 4°, cloth, 460 pp., with 880 illustrations. Baltimore: The Williams and Wilkins Company, 1951. $11.00.

This atlas should be in all collections on pathology and surgery. The illustrations are excellent and depict the lesions generally met with in daily practice. Extremely rare lesions and the specific pathology of the bone marrow are not included. The atlas is designed primarily for senior medical students and hospital residents, and as a reference source for the general practitioner. The publishing is excellent and the price is reasonable for the type of book.

Paul Ehrlich. By Martha Marquardt. With an introduction by Sir Henry Dale. 8°, cloth, 255 pp., with illustrations and frontispiece. New York, New York: Henry Schuman, 1951. $3.50.

This new biography of Ehrlich covers his whole life span and is in part based on the author's previous book, "*Paul Ehrlich als Mensch und Arbeiter*" (1924), which covers the period of thirteen years during which Dr. Marquardt was associated with Ehrlich. The lack of an index for reference purposes is regrettable. The book should be in all medical history collections.

Fundamentals of Clinical Fluoroscopy: With essentials of roentgen interpretation. By Charles B. Storch, M.D., adjunct, Radiodiagnostic Department and Radiotherapy Department, Beth-El Hospital, Brooklyn, New York. 4°, cloth, 196 pp., with 217 illustrations. New York, New York: Grune and Stratton, 1951. $6.75.

The author in this new manual has summarized his own personal experience and the lectures he has given to interns and hospital residents. The material is well arranged, the illustrations are excellent; there is a bibliography and an index. The publishing is well done. The book well deserves a place in collections on the subject.

Primer on Fractures. Prepared by the Special Exhibit Committee on Fractures in Co-operation with the Committee on Scientific Exhibits of the American Medical Association. Sixth edition. 8°, cloth, 109 pp., with 48 illustrations. New York, New York: Paul B. Hoeber, Inc., medical book department of Harper and Brothers, 1951. $2.00.

This manual has been revised to conform to the standard set by the Committee. The use of the terms "open" and "closed" has been permanently established and "compound" and "single" discarded as meaningless. The primer should be in all collections on fractures.

Rest and Pain. By John Hilton, F.R.S., F.R.C.S. Edited by E. W. Walls, M.D., Ch.B., B.Sc., professor of anatomy in the University of London at Middlesex Hospital Medical School, and Elliot E. Philipp, M.A., M.B., B.Chir., M.R.C.S., M.R.C.O.G. With the collaboration of H. J. B. Atkins, D.M., M.Ch., F.R.C.S., director of the Department of Surgery, Guy's Hospital. 8°, cloth, 503 pp., with 105 illustrations. Philadelphia: J. B. Lippincott Company, 1950. $10.00.

The classic treatise of John Hilton, first published in London in 1863, has been reproduced in its entirety. The editor has added a series of short articles to bring the material up to date and there is a short biography and a biographical index. The publishing is excellent and the book should be in all medical libraries.

Exotische Krankheiten und Krankheitsverläufe. Von Dr. Med. F. O. Höring, Apl. Prof. für Innere und Tropenmedizin an der Universität Tübingen, Chefarzt der inneren Klinik des Stadtkrankenhauses Worms a. Rh. 8°, cloth, 407 pp., with 51 illustrations. Stuttgart: Georg Thieme, 1950. Ganzleinen DM 36./ $8.55.

This new book on tropical medicine discusses in order acute infectious diseases, acute cyclical general infections, the chronic reticuloendothelioses, internal and other diseases and their relation to geographical pathology. The material is well arranged, the book is well published, there is a good index and the volume should be in all collections on the subject.

Klinische Chemie und Mikroskopie: Ausgewählte Untersuchungsmethoden für das medizinisch-chemische. Laboratorium. Von Dr. Lothar Hallmann. Sixth edition. 8°, cloth, 594 pp., with 166 illustrations and 7 colored plates. Stuttgart: Georg Thieme, 1950. Ganzleinen DM 24.60/ $5.85.

This new edition of a standard German textbook, first published in 1939, has been thoroughly revised to bring it up to date. There is a short bibliography of the late literature on quantitative methods and a comprehensive index.

Zur Frage der Cortison-Wirkung (Die "corticogene Kettenreaktion"). Von Prof. Dr. W. Beiglböck, Dr. H. Hoff und med. R. Clotten. 8°, paper, 142 pp., with illustrations. Augsburg: Privately printed, 1950. 650. DM.

This small monograph presents the authors' experiments with the new treatment of rheumatic diseases. There is a bibliography of twenty pages. The pages are mimeographed, which accounts for the low price of the book. It should be in all collections on the subject.

NOTICES

COUNCIL OF THE NEW ENGLAND STATE MEDICAL SOCIETIES

The Council of the New England State Medical Societies will hold its usual spring meeting at the Copley Plaza Hotel, Boston, on Sunday, April 15.

PROGRAM

2:30 p.m. Call to order by the President and address of welcome. Roland E. McSweeney, M.D.

Report of the Executive Secretary, including financial report of the Council.

Discussions by the presidents of the six New England State Medical Societies:

- The Practice of Osteopathy in the State of Maine and Its Relationship to the Practice of Medicine. Foster C. Small, President, Maine Medical Association.
- How the State of New Hampshire Answered Its Needs for Physicians in Rural Communities. Harris E. Powers, President, New Hampshire Medical Society.
- The Relation of a State Medical Society to a State University Medical School. Elbridge E. Johnson, President, Vermont State Medical Society.
- State Planning for Medical Service in Civil Defense. Leland C. McKittrick, President, Massachusetts Medical Society.
- Operation of a State Disability Compensation Law. Charles J. Ashworth, President, Rhode Island Medical Society.
- Changes in Connecticut Medical Service Contract and Operation. Thomas J. Danaher, President, Connecticut State Medical Society.

Report of Nominating Committee.

Election of officers (President, Vice-President and Executive Secretary).

Council dinner.

After-dinner speaker:

The Present Emergency and Its Impact on Public Higher Education. Albert N. Jorgensen, President, University of Connecticut.

NEW ENGLAND DEACONESS HOSPITAL

The following clinics will be given in the Baker classroom of the New England Deaconess Hospital at 8:15 a.m.

April 13 — Pregnancy and Diabetes. Drs. Priscilla White and H. Bristol Nelson.

April 20 — The Insulins. Dr. Alexander Marble.

Physicians are cordially invited to attend.

NAVAL RESERVE VOLUNTEER MEDICAL UNIT NO. 1-1

Meetings of the Naval Reserve Volunteer Medical Unit No. 1-1 will be held at the Children's Hospital, 300 Longwood Avenue, Boston, at 7:30 p.m., on the following dates:

April 11 — Some Thoughts on Mobilization. Thomas R. Goethals, Brigadier General.

April 25 — The Diagnosis and Treatment of Intestinal Protozoa. Thomas H. Weller, M.D., associate professor of tropical public health, Harvard Medical School.

Physicians and medical students are cordially invited to attend.

GREATER BOSTON MEDICAL SOCIETY

A meeting of the Greater Boston Medical Society will be held in the auditorium of the Beth Israel Hospital on Wednesday, April 18, at 8:15 p.m. A symposium on common orthopedic conditions in general practice will be presented. Dr. Armin Klein will be chairman. The subjects and speakers will be as follows:

Shoulder Girdle Pain of Cervical Nerve Root Origin (Radiculitis). Meier Karp, M.D.

Subdeltoid Bursitis. Robert Ulin, M.D.

Ruptured Superspinatus Tendon. Samuel S. Hanflig, M.D.

The Frozen Shoulder. Louis Nathan, M.D.

Slipped Capital Femoral Epiphysis — Newer Treatment. Armin Klein, M.D.

Physicians are cordially invited to attend.

MASSACHUSETTS PHYSICIANS ART ASSOCIATION

The annual meeting of the Massachusetts Physicians Art Association will be held on Monday, April 16, at 8 p.m., at the studio of George Aarons, 35 Coolidge Street, Brookline. There will be a short business meeting, with election of officers for the coming year and plans for the annual exhibition.

SPRINGFIELD ACADEMY OF MEDICINE

A meeting of the Springfield Academy of Medicine will be held in the Woman's Club Building, 43 Spring Street, on April 10 at 8:30 p.m. Dr. Elmer Hess, president of the American Urological Association, will speak on the subject "Urology for the General Practitioner."

NEW ENGLAND SOCIETY OF ANESTHESIOLOGISTS

A regular meeting of the New England Society of Anesthesiologists will be held in the auditorium of Bishop McAuliffe Lying-In Pavilion at St. Francis Hospital, Hartford, Connecticut, on Tuesday, April 10.

Program

5:30 p.m. Dinner at the Bond Hotel.

7:30 p.m. Business meeting.

8:00 p.m. Scientific meeting.

Methoxamine and Relation to Anesthesia. William K. Bannister, M.D.

The Use of Relaxants for Intubation. David Little, M.D. Present Status of Intravenous Procaine. Stevens J. Martin, M.D.

SOCIETY MEETINGS AND CONFERENCES

April 7. Massachusetts Society of Anesthesiologists. Page 346, issue of March 1.

April 7–28. Springfield Hospital. Page 421, issue of March 15.

April 9–13. American College of Physicians. Page 296, issue of June 15.

April 10. New England Society of Anesthesiologists. Page 512, issue of September 28.

April 10. Harvard Medical Society. Page 457, issue of March 22.

April 10. Springfield Academy of Medicine. Notice above.

April 10. New England Society of Anesthesiologists. Notice above.

April 11. Naval Reserve Volunteer Medical Unit No. 1–1. Page 535.

April 11. Tufts Medical Alumni Association. Page 422, issue of March 15.

April 12. The Diagnosis and Treatment of Kidney Diseases in Childhood. Dr. Charles A. Janeway. Pentucket Association of Physicians. 8:30 p.m. Haverhill.

April 13. New England Deaconess Hospital. Page 535.

April 15. Council of the New England State Medical Societies. Page 535.

April 16. Massachusetts Physicians Art Association. Notice above.

April 18. Greater Boston Medical Society. Page 535.

April 18. Physical Medicine and Rehabilitation in Psychiatry. Dr. Walter E. Barton. New England Society of Physical Medicine. Hotel Kenmore. 8 p.m.

April 20. Niles Memorial Lecture. Page 458, issue of March 22.

April 20. Boston Surgical Society. Page 494, issue of March 29.

April 20. New England Deaconess Hospital. Page 535.

April 21. Massachusetts Association of Medical Technologists. Page 494, issue of March 29.

April 24. Norfolk District Medical Society. Page 629, issue of October 19.

April 25. Naval Reserve Volunteer Medical Unit No. 1–1. Page 535.

April 28. American Psychosomatic Society. Page 198, issue of February 1.

April 28. Alumni Association, Long Island College of Medicine. Page 458, issue of March 22.

May 7–11. National League of Nursing Education. Page 384, issue of March 8.

May 8. New England Society of Anesthesiologists. Page 512, issue of September 28.

May 9. Norfolk District Medical Society. Page 629, issue of October 19.

May 16. New England Obstetrical and Gynecological Society. Hillcrest Country Club, Leicester, Massachusetts.

May 16–18. American Association of Genito-Urinary Surgeons. Page 160, issue of January 25.

May 21–25. International Society of Orthopaedic and Traumatic Surgery. Page 422, issue of March 15.

May 22–24. Massachusetts Medical Society. Annual meeting. Hotel Statler, Boston.

May 24–26. American Goiter Association. Page 384, issue of March 8.

June 7–10. American College of Chest Physicians. Page 494, issue of March 29.

June 9 and 10. American Society for the Study of Sterility. Page 274, issue of February 15.

June 11–15. American Medical Association. Annual Session. Atlantic City, New Jersey.

June 15–17. American Electroencephalographic Society. Page 346, issue of March 1.

June 20–23. American Orthopaedic Association. Page 422, issue of March 15.

September 4–8. American Congress of Physical Medicine. Page 238, issue of February 8.

September 19. American Medical Writers' Association. Page 1066, issue of December 28.

September 19–21. Mississippi Valley Medical Society. Page 1066, issue of December 28.

September 30–October 2. New Hampshire Medical Society. Annual Meeting. Equinox House, Manchester, Vermont.

October 31. New England Obstetrical and Gynecological Society. Hotel Somerset, Boston.

November 10–21. Pan-Pacific Surgical Association. Page 680, issue of October 26.

July 8–11, 1952. Thirteenth British Congress of Obstetrics and Gynaecology. Page xv, issue of December 14.

District Medical Societies

HAMPSHIRE

May 2. 4:30 p.m. Annual meeting. Jones Library, Amherst.

NORFOLK

April 24. Boston Medical Library. 8 Fenway. 8:00 p.m.

May 9. Annual dinner.

Calendar of Boston District for the Week Beginning Thursday, April 12

Thursday, April 12

*9:00–10:00 a.m. Grand rounds. Robert Breck Brigham Hospital.
*9:00–11:00 a.m. Medical grand rounds. Joseph H. Pratt Diagnostic Hospital.

Friday, April 13

*8:15 a.m. Clinic. New England Deaconess Hospital.
*9:00–10:00 a.m. Medical conference. Joseph H. Pratt Diagnostic Hospital.
*9:00 a.m.–12:00 m. Combined medical and surgical staff rounds. Peter Bent Brigham Hospital.
*10:00 a.m. Surgical clinic. South End Health Unit, 57 East Concord Street, Boston.
12:00 m.–1:00 p.m. Clinicopathological conference (Boston Floating Hospital.) Joseph H. Pratt Diagnostic Hospital.
*12:00 m.–1:30 p.m. Surgical pathologic conference. Joseph H. Pratt Diagnostic Hospital.
*1:30 p.m. Tumor clinic. Outpatient Department, Mount Auburn Hospital, Cambridge.
*2:00–4:00 p.m. Therapeutic conference. Joseph H. Pratt Diagnostic Hospital.
*4:00–6:00 p.m. X-ray conference. Joseph H. Pratt Diagnostic Hospital.

Saturday, April 14

*9:00–10:00 a.m. Surgical grand rounds. Joseph H. Pratt Diagnostic Hospital.

Sunday, April 15

2:30 p.m. Council of the New England State Medical Societies. Copley Plaza Hotel.

Monday, April 16

*11:30 a.m.–12:15 p.m. Clinical conference. South End Health Unit, 57 East Concord Street, Boston. Dr. Cleaveland Floyd in charge.
*12:15–1:15 p.m. Clinicopathological conference. Main Amphitheater, Peter Bent Brigham Hospital.
8:00 p.m. Massachusetts Physicians Art Association. Studio of George Aarons, 35 Coolidge Street, Brookline.

Tuesday, April 17

*9:00–10:00 a.m. Medical conference. Joseph H. Pratt Diagnostic Hospital.
*12:15–1:15 p.m. Clinicoroentgenological conference. Peter Bent Brigham Hospital.
*1:30–2:30 p.m. Pediatric rounds. Burnham Memorial Hospital for Children, Massachusetts General Hospital.

Wednesday, April 18

*9:00–10:00 a.m. Medical conference. Joseph H. Pratt Diagnostic Hospital.
*11:00 a.m.–12:00 m. Medical clinic, including psychiatric conferences. (Children's Medical Center.) Amphitheater, Children's Hospital.
*12:00 m. Medical discussion. Margaret Jewett Hall, Mount Auburn Hospital, Cambridge.
*12:00 m.–1:00 p.m. Clinicopathological conference. (Children's Medical Center.) Amphitheater, Peter Bent Brigham Hospital.
*2:00–3:00 p.m. Combined clinic of all services. (Children's Medical Center.) Amphitheater, Children's Hospital.
*8:15 p.m. Greater Boston Medical Society. Beth Israel Hospital.

*Open to the medical profession.